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SUBACUTE BACTERIAL ENDOCARDITIS

Experiences During the Past Decade

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THE PURPOSE of this paper is to present experience with subacute bacterial endocarditis as it was encountered at the University Hospital, Ann Arbor, Mich., from June 1934 to May 1945. This period begins at a time when no effective treatment was available for this disease, includes the advent of sulfonamide therapy and the more frequently successful combination of sulfonamide compounds with fever induced by administering bacterial vaccine made from the typhoid bacillus, U. S. P., and closes with the effective use of penicillin, resulting in the recovery of the majority of the patients.

The case records have been grouped according to the type of therapy used. In addition, they have been analyzed in regard to the occurrence of the various important features of the disease. In some instances the difference in the frequency of common findings from that reported by others may be significant.

All patients observed during this period for whom the diagnosis of subacute bacterial endocarditis was clearly established are included in this study. No patient is included if the diagnosis was in doubt or if there was failure to obtain a positive blood culture, unless the presence of the disease was demonstrated at autopsy. There were 165 patients, of whom 58 came to autopsy. Prior to 1942 patients with subacute bacterial endocarditis were cared for by the general medical service; from 1942 to 1945 the treatment of these patients was directed by me. This permitted better evaluation of the methods employed. Follow-up data were obtained on all but 5 of the 165 patients.

CLINICAL FEATURES OF THE DISEASE

The common clinical features of subacute bacterial endocarditis as encountered in this series are presented in table 1. Similar data reported by Libman and Friedberg [1] are given for comparison. The present series reveals a lower incidence of petechiae, Osler's nodes,

1. Libman, E., and Friedberg, C. K.: Subacute Bacterial Endocarditis, New York, Oxford University Press, 1941.

palpable spleen and clubbing of the fingers. There are several explanations for this. Some of the patients were under observation for only a short time and at a period in the illness when some of the well known features of the disease were not present. In addition, it is likely that in recent years the diagnosis of subacute bacterial endocarditis has been made much earlier in the course of the disease, and when therapy is instituted many toxic manifestations of the process are lessened. When patients were subjected to therapy which in itself might account for such manifestations as hematuria and albuminuria, only the conditions present prior to such therapy were included in the analysis. It is

TABLE 1.—*Essential Clinical Features of Subacute Bacterial Endocarditis in One Hundred and Sixty-Five Patients*

Clinical Features	Frequency in This Series, per Cent	Frequency According to Libman and Friedberg [1]
Palpable spleen	46.6	80-90%
Retinitis	20.2	Often
Osler's nodes	28.2	50%
Petechiae	54.0	80%
Janeway's spots	4.3	
Clubbing of fingers	37.4	68%
Embolic phenomena	57.7	
Pallor	52.1	Almost constant
Fever	99.4	Constant
Oral sepsis	42.3	
Hematuria *	40.7	
Albuminuria *	45.3	Almost invariably present
Normal urine *	38.4	
Phagocytic endothelial cells	6.0	Not usually present
Acute embolic onset	6.7	
Auricular fibrillation	1.8	0.9% (1 in 109)
Apparent direct relation to exodontia	13.3	
Apparent direct relation to abortion or puerperium	8.2	

	0-5,000	5,001-10,000	10,001-15,000	15,001-20,000	20,001+
White blood cell count	3.1%	53.4%	30.4%	8.1%	5.0%

	0 M-2.50 M †	2.51 M-4.00 M	4.01 M-6.00 M+
Red blood cell count	10.2%	59.8%	30%

* The specimens of urine were from male patients only.
† "M" means millions.

also true that the appearance of petechiae just prior to death was often not noted on the record unless autopsy was performed and their presence noted. I feel certain that clubbing of the fingers is found in more patients than the 37.4 per cent recorded in this series. Certainly among those patients seen and repeatedly examined by me, this feature was found in at least 50 per cent.

The finding that many of the patients in whom the disease was recognized and treated early had normal urine as shown by repeated analyses was rather striking and surprising.

That transient bacteremia follows dental extractions has been amply proved and emphasized in the literature. An apparently direct relationship to exodontia was found in 13.3 per cent of this series. The connection between abortion or postpartum infection and the onset of

bacterial endocarditis is more difficult to establish. In 2 patients there could be no question about the causal relationship, and in 8.2 per cent of the patients there seemed to be a direct connection between inflammatory disease of the pelvic region and bacterial endocarditis.

Three patients in this series had auricular fibrillation at the time of admission to the hospital. With regard to one of them it could be definitely established that this was present for two years prior to the development of the bacterial endocarditis. In another the auricular fibrillation probably developed after the bacterial endocarditis. The duration of auricular fibrillation in the third patient was unknown, although he had had rheumatic heart disease for twenty-two years.

The onset of the symptoms of endocarditis began with acute embolization, without a previous recent illness, in 11 patients, or 6.7 per cent. Many of these were initially admitted to the neurologic or the neurosurgical service.

In 1 patient fever was absent during the period of hospitalization. This, however, was undoubtedly a terminal manifestation. In 1 patient no cardiac murmur was ever heard. This patient also had repeatedly negative blood cultures. Autopsy revealed bacterial involvement of the pulmonary valve.

Definite evidence of pulmonary embolism was found in 17 of 24 patients with congenital heart disease believed to have communication between the greater and lesser circulatory systems.

White[2] stated that in cases of subacute bacterial endocarditis a leukocyte count of 12,000 to 16,000 is common but that the white blood cell count is "at times recorded even at a normal figure." Christian[3] stated that leukocytosis "is the rule; usually moderate, it may be marked." Kinsella[4] stated that "the white cell count is often between 12,000 and 18,000, although normal counts are not uncommon." Gow[5] wrote that the septicemic state is in general associated with leukocytosis and that in cases of subacute bacterial endocarditis a count varying between 10,000 and 20,000 per cubic millimeter is the rule, but that leukopenia occurs fairly frequently. In our series, it will be noted, 53.4 per cent of the patients had a white blood cell count between 5,001 and 10,000 per cubic millimeter. This has been of importance in teaching students inasmuch as it has been a common observation that students tend to disregard the likelihood of bacterial endocarditis if repeated white

2. White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1944.

3. Osler, W.: Principles and Practice of Medicine, edited by H. A. Christian, ed. 15, New York, D. Appleton-Century Company, Inc., 1944.

4. Kinsella, R. A., in Cecil, R. L.: Textbook of Medicine, ed. 6, Philadelphia, W. B. Saunders Company, 1943.

5. Gow, A. E.: Discussion on the Clinical Significance and Course of Subacute Bacterial Endocarditis, Brit. M. J. 2:307 (Aug. 28) 1920.

blood cell counts are normal. Only 13.1 per cent of the patients had a leukocyte count of over 15,000 per cubic millimeter.

A review of the records of the University Hospital revealed that the hemoglobin content was frequently reported in percentage only, without indication of the standard being used. Consequently, it was necessary to use the total red blood cell count as an index of anemia. Although the color index is frequently less than 1, the total red cell count is probably as reliable an index of the anemia characteristic of this disease as is the hemoglobin value. In 70 per cent of the cases the red blood cell count was below 4,000,000 per cubic millimeter.

RELATION OF DISEASE TO AGE AND SEX

Libman and Friedberg[1] reported that two thirds of their patients were in the third and fourth decades of life. The oldest patient seen by them was 74, and the youngest was 4. The distribution in the present series closely parallels that cited by White.[2] It was found to be: 2.4 per cent from 1 to 10 years, 19.4 per cent from 11 to 20, 36.4 per cent from 21 to 30, 19.4 per cent from 31 to 40, 12.1 per cent from 41 to 50, 6.7 per cent from 51 to 60, 4 per cent from 61 to 70 and 1.2 per cent over 70. In this series 55.8 per cent of the patients were found to be in the third and fourth decades. The youngest patient seen was a 4 year old girl with involvement of the tricuspid valve; no underlying valvular disease was established at autopsy. The oldest patient was a man of 72 with subacute bacterial endocarditis superimposed on a sclerotic aortic valve. One man of 71 had involvement of the mitral and tricuspid valves superimposed on old rheumatic valvulitis.

Blumer[6] found that 60 per cent of 328 patients were males. In this series the distribution was 55.8 per cent males and 44.2 per cent females.

UNDERLYING HEART DISEASE

Christian[3] stated that a study of 150 adults with subacute bacterial endocarditis showed rheumatic heart disease to be the underlying condition in 90 per cent. White[2] wrote that rheumatic heart disease was the predisposing factor in about 80 per cent and congenital heart disease in about 5 per cent. In the present series the percentage distribution found, on the basis of clinical diagnoses, was: rheumatic heart disease, 66.1; congenital heart disease, 15.2; both rheumatic and congenital heart disease, 1.2 (2 patients); arteriosclerotic heart disease, 0.6; syphilitic heart disease, 1.8; myocardial infarction, 0.6; unknown underlying disease or none, 13.9. In comparsion, the percentages when only patients examined post mortem (58) were considered were:

6. Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**:105 (May) 1923.

rheumatic heart disease, 60.3; congenital heart disease, 13.8; both congenital and rheumatic heart disease, 3.4; arteriosclerotic heart disease, 1.7; syphilitic heart disease, 3.4; unknown underlying disease or none, 17.2. One of the patients listed as having congenital heart disease had an interauricular septal defect, and although all the valves were involved in the bacterial endocarditis, the margins of the septal defect were normal; there was no evidence of other underlying heart disease. It is not believed that the high percentage listed under "unknown or none" represents bacterial endocarditis superimposed on previously normal valves. It is possible that in rare instances subacute bacterial endocarditis may have developed in previously normal valves, but in the majority of this group preexisting heart disease was present but not classifiable on the basis of the observations made at autopsy. The listing of 1 patient as having myocardial infarction as the predisposing factor is based on clinical information only. It was known that a precordial systolic murmur appeared, following a posterior infarction, seven years prior to the patient's bacterial endocarditis. No other murmur was ever heard.

PATHOLOGIC AND BACTERIOLOGIC ASPECTS

The distribution of the bacteria observed in blood cultures in 157 of the 165 cases of subacute bacterial endocarditis is given in table 2. In 8 of the 165 cases no blood cultures were made during life, and the diagnosis was made only at autopsy. In 7 instances the antemortem

TABLE 2.—*Results of Culture of Blood in One Hundred and Fifty-Seven Cases of Subacute Bacterial Endocarditis* *

Streptococcus Viridans (Alpha)	Streptococcus Hemolyticus (Beta)	Streptococcus Anhemolyticus (Gamma)	Grampositive Cocci in Chains	Gaffkya Tetragena (Micrococcus Tetragenus)	Gramnegative Pleomorphic Rods	Staphylococcus Albus	Staphylococcus Aureus	Brucella Abortus	Clostridium	Negative, but Positive at Autopsy
126	3	12	3	1	1	1	1	1	1	7
80.2%	1.9%	7.6%	1.9%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	4.5%

* In 8 of the 165 cases blood cultures were not made, the diagnosis being made at autopsy only.

blood cultures were negative, but positive cultures were obtained from the heart's blood at autopsy. Since postmortem blood cultures are notoriously unreliable, as a terminal bacteremia with mixed organisms is not uncommon, these cases have not been included in the tabulation. In 4 of them hemolytic streptococci and in 1 gamma streptococci were isolated. It is entirely possible that the instance in which gram-negative pleomorphic rods were isolated represented an infection with the Pfeiffer bacillus.

Whether or not the hemolytic streptococci in 4 of the 7 postmortem blood cultures represented the actual causative agent cannot be definitely stated.   The 3 instances in which hemolytic streptococci were isolated ante mortem are included because the clinical course and features in each were those of subacute bacterial endocarditis.   The 1 case of endocarditis due to Staphylococcus aureus is presented under the heading "Results with Penicillin."   As stated under that heading, the clinical appearance was that of the subacute form of bacterial endocarditis.

The Clostridium isolated was from a patient treated with penicillin. This patient presented the typical picture of subacute bacterial endocarditis superimposed on rheumatic heart disease, but the blood cultures were persistently negative during life.   The terminal symptoms were suggestive of acute myocardial infarction.   At autopsy, the aortic cusps had vegetations, and there were purulent mycotic aneurysms of the coronary arteries.   The Clostridium was isolated both from the center of the partially fixed (solution of formaldehyde U. S. P.) aortic vegetations and from the mycotic aneurysms.   Its position within the genus was not determined.

One patient showing endocarditis due to Cryptococcus histolyticus is included neither in the table of blood cultures nor in the series selected for this study, because the endocardial involvement was merely an incidental finding at autopsy in a case of general cryptococcosis.

When studies of strains were done (since 1942), the streptococci of the viridans group were found to be almost always of the salivarius strain.   In connection with the studies of strains, susceptibility was determined in vitro in most instances after 1942.   Occasionally organisms were encountered which could not be grown in proper mediums and under conditions suitable for in vitro studies of susceptibility.   In those cases in which oxophenarsine hydrochloride, neoarsphenamine, acriflavine and congo red were included in the study of inhibition of bacterial growth, inhibition was never produced by concentrations obtainable in vivo. Of the sulfonamide compounds, sulfathiazole generally gave complete inhibition in greater dilution than any others.   In a considerable number of cases, however, the level of inhibition was the same for both sulfathiazole and sulfadiazine.   For 2 patients who were under treatment with sulfathiazole, studies of susceptibility were repeated two to three weeks after the initiation of therapy.   Comparison of the inhibitory levels showed that the organisms had acquired in vitro resistance to the sulfonamide compound being used in therapy but not to other sulfonamide compounds.   This is discussed later.

In the cases of bacterial endocarditis in which autopsy was performed (58) major involvement was found as follows: mitral valve, 21; aortic valve, 10; mitral and aortic valves, 14; interventricular septal

defect and aortic valve, 1; mitral and tricuspid valves and interventricular septal defect, 1; tricuspid and pulmonary valves and interventricular septal defect, 1; pulmonary valve and pulmonary artery, 1; tricuspid valve, 2; aortic valve and ductus arteriosus, 1; aortic and tricuspid valves, 1; aortic and pulmonary valves, 1; mitral and tricuspid valves, 2; mitral, tricuspid, pulmonary and aortic valves, 1; pulmonary, tricuspid and mitral valves, 1.

Recent or old myocardial infarcts or both were found in 25 per cent of the cases in which autopsy was performed. White[2] stated that cardiac infarction is "very rare." In only a few cases was myocardial infarction suspected before death. In 2 cases in which autopsy was not performed there was electrocardiographic evidence of posterior myocardial infarction; one of the patients had suffered his infarction seven years prior to the development of bacterial endocarditis, and one had had anginal pain for six years, although the time of infarction was not known. This would suggest that even in patients successfully treated for bacterial endocarditis, if the disease has been well established, some loss of cardiac reserve may occur beyond that anticipated from the valvular damage. With the known frequency of embolic necroses and small pyemic abscesses in the myocardium at autopsy in cases of subacute bacterial endocarditis, it is not surprising that myocardial infarcts were found so frequently.

RESULTS OF TREATMENT PRIOR TO THE ADVENT OF SULFONAMIDE COMPOUNDS

Prior to the use of sulfonamide compounds, there were 69 patients who either received no treatment aimed at eradicating the infection or were given treatment in general use prior to the advent of sulfonamide therapy. Data on these patients are summarized in table 3.

Many of them received sodium cacodylate. Some received autogenous vaccines. A few were given metaphen intravenously. More than half received one or more blood transfusions. All except 3 are known to have died from subacute bacterial endocarditis. The 3 on whom no follow-up record was obtainable were severely ill at the time of discharge. Two of the 3 were discharged for terminal care at home. These 2 undoubtedly died of the disease, and there is nothing on the record of the third that would suggest recovery as likely.

In a series of 2,596 cases collected from the literature, Lichtman[7] found the incidence of spontaneous recovery to be 1 per cent. In the present series, there was no recovery in the 66 patients in this group on whom follow-up reports were obtained.

7. Lichtman, S. S.: Treatment of Subacute Bacterial Endocarditis, Ann. Int. Med. **19**:787 (Nov.) 1943.

RESULTS WITH SULFONAMIDE COMPOUNDS ALONE

Fifty-three patients were included in this group. There were 2 patients on whom follow-up reports were not obtained. Of the 51 patients whose status was determined, all but 1 were dead. Lichtman[7] arbitrarily defined adequate treatment for this group as a minimum of two weeks of intensive sulfonamide therapy. Thirty-nine patients were so treated. My patients are included in table 3.

TABLE 3.—*Results of Various Forms of Treatment of Subacute Bacterial Endocarditis*

Treatment	Present Series					Lichtmen, 1943[7]		Total Percentage of Recoveries, Both Series
	Patients	Number Known to Be Dead	Number Known to Be Alive	Number on Whom There Is No Follow-Up Report	Adequacy of Treatment	Patients	Number Who Recovered	
Such drugs and forms of therapy as were in use prior to advent of sulfonamide compounds	69	66	0	3	....	2,596	25 (0.96%)	0.94
Sulfonamide compounds only	53*	50	1† (2%)	2	39 had sulfonamide compounds for 2 weeks or more	489	21 (4.3%)	4.2 ‡
Sulfonamide compounds and heparin	5	5	0	..	3 received both for at least 2 weeks	109	7 (6.4%)	6.2 ‡
Sulfonamide compounds and hyperthermia produced with typhoid bacillus vaccine	16	14	2 (12.5%)	..	7 adequately treated by the standards set forth in text; 28.5% of these recovered	45	7 (15.5%)	15.5 (of 58 patients)
Sulfonamide compounds, neoarsphenamine and hyperthermia produced with typhoid bacillus vaccine	8	8	0	..	6 adequately treated by the standards set forth in text; none recovered	....		
Arsenicals alone	2	2	..	..	See text			

* One patient had successful ligation of patent ductus arteriosus without benefit.
† Patient was D. H. (see report of case).
‡ Percentage includes only adequately treated patients from the present series (see text).

The living patient, D. H., is of some interest. He was admitted to the hospital in January 1942, after a grippal type of onset of subacute bacterial endocarditis in November 1941. His condition was diagnosed as an interventricular septal defect with repeated pulmonary infarcts and pleural effusion. The spleen was questionably palpable. Three blood cultures, made at weekly intervals, were positive for Streptococcus viridans, although the patient was receiving sulfadiazine. He received sulfadiazine for twenty-three days, with defervescence, although slight elevations of temperature persisted most of the time. Resolution of some of the pulmonary infarcts was complete, and the more recent ones were resolving at the time of the patient's discharge in February 1942. He was seen in the clinic three weeks later, feeling well but having noted fever on several occasions.

By April 1942 he was feeling well and gaining weight. A roentgenogram in July 1943 revealed no abnormality. A preemployment roentgenogram in October 1943 revealed tuberculosis at the apex of the right lung. He was readmitted to the University Hospital in July 1944 for thoracoplasty. No evidence of subacute bacterial endocarditis was noted while he was in a nearby sanatorium for patients with tuberculosis or during this period in the University Hospital. The cardiac status was otherwise unchanged.

It cannot be definitely stated that his recovery was not spontaneous, but it was probably due to the treatment with sulfadiazine.

A second patient, W. P., was previously observed by Field, Hoobler and Avery [8] and included as recovered in the report of Lichtman.[7] This patient was treated with sulfapyridine in November and December of 1939. He was considered as cured and was as well as ever in April 1941. He died in 1943, and autopsy was performed. Death was apparently due to congestive heart failure. There was evidence of old splenic infarcts and of old and recent renal infarcts. The heart confirmed the clinical diagnosis of the tetralogy of Fallot. An aortic cusp was thickened and slightly granular. Microscopic examination of this cusp showed chronic productive valvulitis with areas of necrosis in the interior of the valve. There were several small foci of greater activity involving the endothelium and the subendothelial supporting tissue. No vegetations were present, but the pathologist felt that active valvulitis was still present. No organisms were demonstrated by Gram's method.

Although this patient did not exhibit the clinical- features generally associated with the bacteria-free stage of subacute bacterial endocarditis and although death from congestive heart failure and pneumonia at 27 in a person with the tetralogy of Fallot is certainly not unusual, the results of autopsy suggest that this represents a bacteria-free stage of the disease.

In Lichtman's report [7] there is mention of a 4 per cent incidence of recovery in 489 patients treated by sulfonamide compounds alone (one of whom was W. P., discussed previously). In the 51 patients whose entire course was known in the present series, recovery resulted in approximately 2 per cent (1 patient). However, an additional patient (W. P.) was clinically well for three years.

RESULTS WITH COMBINED SULFONAMIDE-HEPARIN THERAPY

In 1939 the preliminary report of Kelson [9] on the use of heparin and sulfapyridine increased the hope that bacterial endocarditis might become more amenable to sulfonamide therapy. The later report of Leach and associates [10] was not as encouraging. Lichtman's review [7]

8. Field, H., Jr; Hoobler, S. W., and Avery, N. L., Jr.: Results of Chemotherapy in Subacute Bacterial Endocarditis, Am. J. M. Sc. 202:798 (Dec.) 1941.

9. Kelson, S. R.:. A New Method of Treatment of Subacute Bacterial Endocarditis Using Sulfapyridine and Heparin in Combination, J. A. M. A. 113:1700 (Nov. 4) 1939.

of 1943 includes a total of 109 patients treated with heparin and sulfonamide compounds, with an incidence of recovery of 6.5 per cent. Lichtman arbitrarily defined adequate treatment as at least two weeks of intensive sulfonamide medication together with two weeks of heparinization with a blood coagulation time of one hour.

The present series includes only 5 patients treated according to the method (table 3), all of whom died. The group is extremely small because of general dissatisfaction with the method at the University Hospital.

RESULTS WITH COMBINED SULFONAMIDE-FEVER THERAPY

White and Parker [11] reported in 1938 that the effect of sulfanilamide on beta hemolytic streptococci in vitro was enhanced by elevated temperatures. This was followed by a further report by White [12] in 1939 on the relationship between temperature and the streptococcidal activity of sulfanilamide and sulfapyridine in vitro. It was shown that under the stated conditions beta hemolytic streptococci are much more susceptible to sulfanilamide and sulfapyridine at from 39 to 40 C. than they are at 37 C.

Sherman [13] had previously shown that some strains of Streptococcus salivarius are not as resistant to heat as other viridans streptococci.

Lichtman's report of 1943 [7] includes 61 patients treated with artificial hyperthermia and sulfonamide compounds, with a recovery rate of 6.5 per cent. In the same report he mentioned 45 patients treated with combined chemotherapy and hyperpyrexia produced by intravenous administration of bacterial vaccine made from the typhoid bacillus, U.S.P., with an incidence of recovery of 15.5 per cent.

There were 16 patients in the present series who were treated by chemotherapy and pyretotherapy combined. Fever was produced by intravenous administration of bacterial vaccine made from the typhoid bacillus, U. S. P. Before the use of the continuous intravenous drip of the vaccine in isotonic solution of sodium chloride, milk was given intramuscularly about four hours before the administration of the vaccine in an attempt to prolong the peak temperature without multiple injections of the vaccine. A definite program of management for these

10. Leach, C. E.; Faulkner, J. M.; Duncan, C. N.; McGinn, S.; Porter, R. R., and White, P. D.: Chemotherapy and Heparin in Subacute Bacterial Endocarditis, J. A. M. A. **117**:1345 (Oct. 18) 1941.

11. White, H. J., and Parker, J. M.: The Bactericidal Effect of Sulfanilamide upon Beta Hemolytic Streptococci in Vitro, J. Bact. **36**:481 (Nov.) 1938.

12. White, H. J.: The Relationship Between Temperature and the Streptococcidal Activity of Sulfanilamide and Sulfapyridine in Vitro, J. Bact. **38**:549 (Nov.) 1939.

13. Sherman, J. M.: The Streptococci, Bact. Rev. **1**:3 (Dec.) 1937.

patients was developed, with the result that there was a gratifying degree of tolerance for the periods of hyperpyrexia. It was found that the rigor can be largely suppressed, the cyanosis prevented, the pulse rate lowered and the discomfort decreased by administration·of 100 per cent oxygen by the Boothby mask. This has no effect on the febrile response. The administration of oxygen was started about fifteen minutes before the anticipated time of the rigor. It was discontinued before the appearance of diaphoresis. Data on these patients are summarized in table 3.

At the time these patients were being treated, some of the house physicians felt that the method was not receiving a fair trial inasmuch as no selection of patients was practiced. However, since it was felt that the method was the best that could be offered, all patients who were able to tolerate a single session of hyperthermia were so treated. Despite the obviously hopeless condition of some, it was remarkable how well the treatment was tolerated by most of the patients. One patient died, apparently of exhaustion, on the day following his twelfth paroxysm of fever, which was unusually prolonged and severe.

In an attempt to evaluate the results better, the group has been divided into patients adequately and patients inadequately treated. Adequate treatment has been arbitrarily defined as a minimum of thirty-two hours of fever with the temperature at or above 103 F., produced by at least nine paroxysms, with maintenance of the generally accepted therapeutic blood levels of the sulfonamide compounds used—5 to 10 mg. per hundred cubic centimeters for sulfathiazole and 10 mg. per hundred cubic centimeters for sulfadiazine. Some of the patients who might have tolerated adequate treatment as so defined did not receive it for various reasons. The maximum number of hours of induced fever with the temperature at or above 103 F. was fifty, given by thirteen inductions.

Both of the patients who recovered had rheumatic heart disease. One, whose bacterial endocarditis was of about two months' duration, was treated in 1941. He was in excellent health after this therapy and was followed until January 1945. The second patient, whose disease was of four months' duration, was treated in 1942. She was followed until January 1945 and remained entirely well. After their initial discharge, both were subsequently readmitted on two occasions for exodontia with prophylactic chemotherapy.

RESULTS WITH COMBINED SULFONAMIDE-NEOARSPHENAMINE-FEVER
THERAPY

In May 1942, Osgood[14] reported on the use of neoarsphenamine in the treatment of subacute bacterial endocarditis and severe systemic·

14. Osgood, E. E.: Neoarsphenamine Therapy of Bacterial Infections, Arch. Int. Med. **69**:746 (May) 1942.

staphylococcic infections. In his article he suggested combining hyperthermia with neoarsphenamine, and with sulfonamide compounds as well, if the organism showed susceptibility to both sulfonamide compounds and neoarsphenamine in bone marrow cultures. He reported promising results.

Table 3 summarizes the results obtained when neoarsphenamine, sulfonamide compounds and bacterial vaccine made from the typhoid bacillus, U. S. P., were used in conjunction. Here, too, the group was divided into patients who received adequate and those who received inadequate treatment. Adequate treatment was arbitrarily defined as including a minimum of thirty-two hours of fever with the temperature at or above 103 F., induced by at least nine paroxysms, maintenance of the generally accepted therapeutic blood levels of the sulfonamide compounds and administration of at least one course of neoarsphenamine as outlined by Osgood for the treatment of bacterial endocarditis, namely, 0.8 mg. of neoarsphenamine per pound of body weight every four hours for four doses on the first day and then every eight hours for a total of six days.

None of these patients recovered. Complications due to the treatment with neoarsphenamine occurred in 3 of the 8 patients.

In addition to the 8 patients reported on in table 3, 2 patients received arsenicals alone. The one received adequate neoarsphenamine therapy as recommended by Osgood, and the other received 1,200 mg. of oxophenarsine hydrochloride during five days for syphilis. The latter patient refused treatment for his bacterial endocarditis. Both patients died of their disease. Data on them have been included, under a separate heading, in table 3.

If an attempt is made to evaluate the effectiveness of the combined sulfonamide-fever therapy, the patients adequately treated with this therapy may be combined, as indicated in table 3, with those patients receiving adequate sulfonamide-neoarsphenamine-fever therapy. This can be done inasmuch as neoarsphenamine had no beneficial effect. It cannot be stated that it may not have had a deleterious effect on the sulfonamide-fever therapy, but there is no published evidence to suggest this. By combining the two adequately treated groups, one finds that 2 of the 13 patients recovered (15.4 per cent). This is, of course, too small a group to have any statistical significance, but the figure is in striking agreement with Lichtman's 15.5 per cent recovery of 45 patients.

RESULTS WITH PENICILLIN

Because of the rigid control of penicillin and the high military priority, amounts adequate for clinical use in the treatment of subacute bacterial endocarditis were not soon available. Early reports, known to all,

were indeed discouraging. However, with the report of Loewe, Rosen-blatt, Greene and Russell [15] in January 1944, interest in penicillin therapy of bacterial endocarditis was revived. In addition, the supply of penicillin for civilian use was then increased.

Table 4 summarizes the results obtained at the University Hospital with the use of penicillin. Of the 12 patients who received this antibiotic agent, 7 experienced an apparently successful result.

Even in this small group of patients it became apparent that the continuous intravenous drip method of administration was not satisfactory. This method was attempted in 6 cases, and in only 2 was it tolerated for fourteen days. Thrombophlebitis occurred in every patient receiving penicillin solutions by continuous intravenous drip.

At this hospital experience with mixtures of yellow wax, peanut oil and penicillin was disappointing. Considerable difficulty was found in getting uniform preparations, and at times the penicillin was found to have separated from the emulsion. In addition, the nurses complained about the difficulty of drawing the emulsion from the vial and administering it through any gage of needle less than no. 18. It was felt also that the introduction of oil-wax-penicillin mixtures was not without danger of future complications in the form either of "paraffinomas" or of sensitization phenomena.

Intermittent intramuscular or subcutaneous administration of penicillin was satisfactory except for the obvious discomfort caused the patient and the interference with rest.

Early in 1945 the continuous intramuscular drip method was employed. In practice this was sometimes a deep subcutaneous infusion. The desired daily dose of penicillin was diluted in 750 to 1,000 cc. of isotonic solution of sodium chloride or 5 per cent dextrose solution and injected into the thigh through a 21 gage needle. A pillow placed lateral to the selected thigh left the patient free to move normally in bed, and there was no interference with sleep. Regulation of the speed of hypodermoclysis was simple. If about twenty or more hours were utilized for administration, there was little discomfort from distention of the tissue, and nursing care, such as bathing and back rubs, could be given during the hours when penicillin was not being administered. No complications were encountered.

The smallest total dose of penicillin resulting in apparent cure was 2,540,000 units. The largest total dose administered was 21,640,000 units. The patient who received the latter dose had been ill for over a year and experienced occasional embolic episodes. Later, the emboli

15. Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, J. A. M. A. **124**:144 (Jan. 15) 1944.

TABLE 4.—*Data on Patients with Subacute Bacterial Endocarditis Treated with Penicillin*

Patient	Preexisting Lesion of Heart	Probable Date of Onset of Subacute Bacterial Endocarditis and Duration Prior to Administration of Drug	Previous Treatment	Organism in Blood Culture	Susceptibility Expressed as Concentration of Drug Required to Produce Complete Inhibition	Treatment *	Outcome †
J. H., discharged 7/27/44	Rheumatic heart disease, mitral stenosis, mitral insufficiency	? Jan. 1944 (5 mo.)	?	Str. salivarius 1/3/45 neg. 5/23/45 neg.	0.0001 units per cc.	2.8 M penicillin cont. IV for 14 days; 1.395 M penicillin IM for 9 days; total, 4.195 M	Cured; patient entirely well, 1/10/46
H. S., discharged 9/2/44	Congenital heart disease, patent ductus arteriosus	? Jan. 1944 (7 mo.)	?	Str. salivarius	?	1.2 M penicillin cont. IV for 7 days; 2.845 M penicillin IM for 19 days; total, 4.045 M; sulfadiazine for 44 days	Apparently cured; nephritis continues; well, June 1945
C. K., discharged 4/29/44	Congenital heart disease, ? septal defect	? Summer of 1942 (20 mo.)	None	Str. salivarius 11/1/44 neg.	?	2.0 M penicillin cont. IV for 14 days; sulfadiazine for 2 days	Apparently cured
F. G., discharged 10/30/44	Rheumatic heart disease, aortic insufficiency, mitral stenosis, mitral insufficiency, auricular fibrillation	? June 1944 (2 mo.)	Sulfadiazine	Str. salivarius 3/31/45 neg.	0.01 unit per cc.	8.01 M penicillin IM for 52 days; typhoid vaccine IV, four times	Arrested
M. F., died 12/2/44	Rheumatic heart disease, mitral insufficiency	Jun. 1944 (11 mo.)	Sulfonamide compounds	Str. salivarius	0.1 unit per cc.; none with sulfadiazine	1.33 M penicillin IM for 11 days	Death (cerebral embolus)
G. B., discharged 1/12/45	Rheumatic heart disease, mitral stenosis, mitral insufficiency	? Jan. 1944 (11 mo.)	Sulfonamide compounds, 1,380,000 units of penicillin	Str. salivarius, nonhemolytic streptococci	0.1 unit per cc.; none with sulfathiazole or sulfadiazine	7.002 M penicillin IM for 50 days	Death, ? nephritic

Patient	Diagnosis	Onset (age)	Previous treatment	Organism	Concentration	Treatment	Result
N. S., died 7/27/44	Rheumatic heart disease, aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency	? July 1943 (19 mo.)	Sulfadiazine, 2 days	None	?	Cont. IV penicillin 200,000 units per 24 hr. for 5 days; 15,000 units IM every 2 hr. for 6 days; total, 1.78 M in 11 days	Death, subacute bacterial endocarditis at autopsy
E. B., discharged 8/6/44	Congenital heart disease, patent ductus arteriosus	? Jan. 1943 (10 mo.)	?	Str. salivarius 1/9/45 neg. 5/23/45 neg.	0.1 unit per cc.	Ligation of patent ductus arteriosus, 11/2/43; sulfonamide compounds and fever; arsphenamine and fever; cont. IV penicillin, 2.8 M for 13 days; 10.0 M IM for 60 days; total, 12.8 M penicillin in 73 days; typhoid bacillus vaccine fever, 3 days	Cured; patient entirely well, 1/3/46
D. W., discharged 5/27/44	Congenital heart disease, ? tetralogy of Fallot	March 1944 (6 wk.)	Sulfonamide compounds	Str. salivarius	0.0001 unit per cc.	Cont. IV penicillin for 8 days; penicillin IM for 7 days; total, 2.54 M in 15 days	Apparently cured; patient entirely well, April 1945
V. G., discharged 5/1/45	Rheumatic heart disease, aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency	? Jan. 1944 (12 mo.)	1,500,000 units penicillin, May 1944; 1,200,000 units, June 1944; 1,200,000 units, July 1944; 1,100,000 units, plus heparin, Sept. 1944	Str. viridans	0.1 unit per cc.; none with sulfathiazole or sulfadiazine	Total, 21.64 M penicillin in 106 days	Death, 3 mo. after discharge, presumably due to cerebral embolus
T. M., died 3/15/45	Rheumatic heart disease, mitral stenosis, mitral insufficiency	July 1944 (8 mo.)	None	Str. salivarius	?	Cont. subcutaneous penicillin for 9 days; total, 3.08 M; sulfamerazine 3 Gm. a day for 8 days	Death (cerebral embolus)
J. M., discharged 5/20/45	Rheumatic heart disease, mitral stenosis, mitral insufficiency	Jan. 27, 1945 (5 wk.)	None	Staph. aureus	?	Sulfathiazole for 14 days; cont. subcut. penicillin for 31 days; intermittent IM penicillin 7 days; total, 11.56 M in 38 days	Arrested; patient well and working, Sept. 1945

* M stands for million units; cont. IV, for continuous intravenous drip; IM, for intramuscular injections.
† If the patient presented no symptoms at three months, the disease was considered ? arrested; from three to six months, arrested; from six to twelve months, apparently cured, and from twelve months on, cured.

apparently became sterile. Prior to discharge she suffered several small embolizations without apparent sequelae.

The percentage of initially good results obtained in this group of 12 patients is 58.3. In reports of 98 cases collected from the literature 70.4 per cent of patients are said to have recovered. By combining the two groups, one obtains a recovery rate of 69 per cent for 110 patients. These figures do not include patients reported on during the period of inadequate supply of penicillin:

Two of the patients in the penicillin-treated group are of unusual interest.

One patient, E. B., was admitted to the hospital, Oct. 13, 1943, with a patent ductus arteriosus and a history of fever since January 1943. During this ten month period she had had her antrums needled in February, an abscessed tooth extracted in March and a Caldwell-Luc operation on the left antrum in July. Blood cultures made at another hospital in September were "positive." The ductus arteriosus was ligated at the University Hospital three weeks after the patient's admission. Blood cultures made before and after the operation were positive for Str. salivarius. Despite treatment with sulfonamide compounds and combined therapy with neoarsphenamine, sulfonamide compounds and fever, the blood cultures remained positive although the patient seemed to maintain a fairly good clinical condition. After several unsuccessful attempts to secure penicillin, 2,800,000 units was obtained for continuous intravenous administration. This was started on approximately the four hundredth and eighty-third day of her illness. Severe thrombophlebitis of the veins of the arms developed on the sixth day of administration. Pneumonia developed, and Pseudomonas schuylkilliensis was isolated from the blood and the sputum and also from the penicillin solution in the infusion flask (not from the ampule of penicillin). The course was completed by the intramuscular route. Blood cultures became negative for Str. salivarius. Treatment was concluded on May 12, 1944. During the patient's attack of pneumonia, a caseous mediastinal lymph node evidently broke down, and the sputum became positive for Mycobacterium tuberculosis by concentrate, culture and guinea pig inoculation. Blood cultures again became positive for Str. salivarius, and the intramuscular administration of penicillin (180,000 units a day) was started again on June 6 and continued until August 6. Since then blood cultures have remained sterile. Clinical recovery was prompt and striking. Full activity was gradually undertaken by the patient, without cardiac symptoms or any further evidence of tuberculosis. She was in excellent general condition and without evidence of infection on Jan. 3, 1946.

The second patient of unusual interest was a 21 year old university student who was working as a technician in the medical outpatient laboratory. This girl, J. M., had a tooth extracted without chemotherapy on Feb. 27, 1945. Rheumatic mitral stenosis and insufficiency had developed some years before. Symptoms of bacterial endocarditis developed on April 1. The appearance was that of subacute rather than acute bacterial endocarditis, despite the isolation of Staph. aureus (coagulase positive) in blood cultures. Treatment was instituted on April 5. Every day for the first week 500,000 units of penicillin was given by the continuous subcutaneous drip method. Thereafter the dose was reduced to 300,000 units a day until May 5, when the dose was further reduced. Sulfathiazole was also given during the first fourteen days of treatment. Recovery was

prompt after April 20. The patient completed the academic term, served as a counselor in a summer camp and is now working as a laboratory technician.

<div align="center">COMMENT</div>

In order to approach the therapy of any disease rationally, it is necessary to have a thorough understanding of the pathologic changes produced as well as a knowledge of the characteristics of the causative agent.

There is an abundance of literature on the pathologic aspects of bacterial endocarditis, both natural and experimental. I have found that the articles of Nedzel[16] and Allen[17] are most helpful in giving a basic understanding of the process involved. Libman and Friedberg[1] in their monograph have discussed the pathologic aspects of the naturally occurring disease at some length.

Allen[17] described the vegetations in bacterial endocarditis as consisting of three zones: a proximal layer of fibrin, platelets, red blood cells, white blood cells and necrotic and necrobiotic shreds of valvular elastic and collagenous connective tissue; a middle zone made up largely of bacteria, and an outermost layer of fibrin in which red blood cells and a sprinkling of white blood cells are enmeshed. The major portion of the vegetation underlies the bacteria. Growth of the vegetation may occur both by destructive, ulcerative activity at the base and by deposition of blood elements superficially. Allen commented that the severe necrosis and edema, with separation of the elastic and collagenous fibers, are highly suggestive of a response to an altered local reactivity of tissue. Nedzel's[16] description of the events occurring after the intravenous injection of pitressin similarly suggests altered local reactivity of tissue.

When the diagnosis of bacterial endocarditis can be made early, before the vegetations are large, the lesions may be attacked at both the base and the free surface. In such instances an effective antibacterial agent which does not interfere with the natural body defenses may initiate healing, with a minimum of valvular deformity resulting. It is in this type of lesion that heparin might serve as a worth while adjuvant. By inhibiting further thrombotic activity in zones 1 and 3, heparin might allow healing to occur with less distortion of the valve and a smaller scar.

After the disease is well established and the vegetations are of significant size, the indications for heparin are less apparent. In itself the drug is not antibacterial. It does not dissolve fibrin. It probably does not "loosen" already formed thrombotic material, since embolization itself does not seem to be more frequent with the use of heparin than without it. The healing of such vegetative lesions probably takes

16. Nedzel, A. J.: Experimental Endocarditis, Arch. Path. **24:**143 (Aug.) 1937.

17. Allen, A. C.: Nature of Vegetations of Bacterial Endocarditis, Arch. Path. **27:**661 (April) 1939.

place by fibroblastic proliferation, macrophagocytic activity, leukocytic phagocytosis and endothelial proliferation. Fibrosis may later be followed by calcification. If sterilization of the blood stream can be effected, the deposition of sterile fibrin over the surface of the vegetation may be desirable. Healing may take place, with the invading bacteria being destroyed or, as in tuberculosis, being enclosed in a relatively avascular scar. Such fibrotic lesions might harbor viable organisms for some time, which are prevented from further activity only by their own low virulence and the wall of fibrous connective tissue about them.

If sufficient bacteriostasis is to occur to affect greatly the basilar ulcerative process, it probably must take place by way of the capillaries which have been formed in the affected area rather than by penetration of the thrombus and cellular debris and of the free surface of the vegetation. Hence, it is logical to seek as adjuvants to the antibacterial drug agents which will stimulate the immune forces of the body, promote invasion of the tissue by the leukocytic elements of the blood, accelerate or initiate the activity of fixed tissue macrophages, fibroblasts and angioblasts and increase endothelial proliferation. Such agents will, in short, hasten and stimulate the reparative processes of the body as a whole and of the tissues involved locally. Foreign protein therapy (e. g. the administration of bacterial vaccine made from the typhoid bacillus, U. S. P.) is alleged to have such effects.

Under normal circumstances man is able to clear a large number of bacteria from the blood stream without incident. When bacteria have lodged in tissues with poor local defense and initiated cellular necrosis, they are in part protected by the products of cellular death. Anything which will increase the local defense of the tissues may be helpful. Foreign protein therapy is said to produce a partition of the polymorphonuclear leukocytes, sending more of them out of the blood stream and into the tissues. The activity of the histiocytes is enhanced; they tend to proliferate and migrate to form a subendothelial "polster." Fibroblastic and endothelial cell proliferation may be speeded up. The antibody levels in the blood of patients with subacute bacterial endocarditis are generally good, and little is expected from immunotransfusion in this respect. In those cases in which the opsonocytophagic index was determined for the patient's own organisms, this was increased after the intravenous administration of the vaccine made from the typhoid bacillus.

The enhancement of the antibacterial action of sulfonamide compounds by hyperpyrexia, as reported by White and Parker [11] and by White,[12] has been questioned by Hamilton and Hamilton.[18] In working

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18. Hamilton, B. W., and Hamilton, T. R.: Pathology and Bacteriology of Streptococcus Endocarditis in Relationship to Sulfonamide Chemotherapy:

with viridans streptococci and enterococci, they concluded that sulfathiazole was no more effective in vitro at 40 C. than at 37 C. In some instances it was less effective at elevated temperatures. When they used the Lancefield group A streptococci, their work was confirmatory of that of White.[12] However, some strains of Str. salivarius are not resistant to heat. Since it is this organism which is most frequently encountered in subacute bacterial endocarditis, hyperpyrexia may be of value in some instances. The work of the Hamiltons indicates the advisability of making studies of susceptibility at both 37 and 40 C. Even though fever therapy may at times have no additive effect on the action of the sulfonamide compounds, the beneficial effects of foreign protein therapy probably justify its use. However, in cases in which hyperpyrexia is not beneficial, foreign protein therapy could be given with the avoidance of high temperatures.

The problem of the development of resistance by the agents of disease to the substances which are used to overcome them is an important one. Acquisition of resistance or tolerance to sulfonamide compounds has been repeatedly demonstrated. As previously noted, 2 of the patients in this series, the only 2 who were tested for it, showed the development of specific resistance to sulfonamide compounds in vitro. In 1 instance it required ten times the original bactericidal level to produce this effect, and in the second the degree of resistance was of the order of one hundred times.

Some of the patients who were treated by combined chemotherapy and pyretotherapy were given intensive treatment initially. This was done in the belief that the organisms might rather rapidly develop resistance to the sulfonamide compounds used unless they were destroyed by the drug or by the body defenses plus the bacteriostatic action of the drug. These patients were given large initial doses of sulfathiazole or sulfadiazine to produce a satisfactory blood level rapidly. Fever therapy was then instituted with daily inductions during the first three days. Oral intake of the sulfonamide compound was supplemented by intravenous administration of 2.5 to 5 Gm. of the sodium salt at the time of injection of the vaccine made from the typhoid bacillus. To several, including 1 of the cured patients, whereas sulfathiazole was given by mouth, sulfadiazine sodium was given intravenously.

If any conclusions can be drawn from in vitro studies of susceptibility, it can be said that the streptococci of the viridans type isolated in clinical cases of subacute bacterial endocarditis in the past eighteen to twenty-four months exhibit a degree of resistance to sulfonamide

II. The Effect of Temperature Elevation on the Action of Sulfathiazole upon Endocarditis Strains of Streptococcus Viridans, Enterococci and Group A Streptococci, Am. J. Clin. Path. **14**:502 (Oct.) 1944.

compounds rarely seen in the earlier days of sulfonamide therapy. With the last 6 or 7 patients for whom such studies were made, 3 of whom are included in table 4, no inhibition was obtained with a concentration of sulfadiazine or sulfathiazole of 100 mg. per hundred cubic centimeters. This was so unusual that the studies were repeated numerous times, but always with the same result. From conversations with others making similar studies, I learned that this experience is not unique in this hospital's laboratories. It suggests that the widespread use of sulfonamide compounds has brought about the perpetuation of resistant strains of Str. viridans. It is probably fortunate that penicillin appeared when it did. It is doubtful whether the results of treatment of bacterial endocarditis with sulfonamide compounds would have continued at even the modest level achieved.

There has been published recently evidence that staphylococci may acquire resistance to penicillin in vivo.[19] This resistance may be a permanent characteristic. It is entirely likely that evidence of acquired resistance to penicillin in streptococci will be forthcoming. Consequently, it is extremely important that large initial doses of penicillin should be used in any case of infection in which its use is indicated. At the present time the administration of no less than 500,000 units of penicillin a day is advisable for the first two or three weeks of treatment in bacterial endocarditis. If positive blood cultures persist after three days of treatment, this dose might well be increased to 2,000,000 units a day.

SUMMARY AND CONCLUSIONS

One hundred and sixty-five cases of subacute bacterial endocarditis occurring between 1934 and 1945 have been surveyed with regard to the clinical, bacteriologic and pathologic features of the disease and with particular regard to the results of the various methods of treatment used.

In patients with subacute bacterial endocarditis leukocytosis is as frequently absent as it is present.

The pathology of the disease carries implications as to treatment.

Myocardial infarcts were found in one fourth of the cases in which autopsy was performed.

None of the 66 untreated patients recovered.

Recovery occurred in 2 per cent of 53 patients treated with sulfonamide compounds alone.

Two (15.4 per cent) of 13 patients adequately treated by combined chemotherapy and pyretotherapy were cured.

19. Spink, W. W.; Hall, W. H., and Ferris, V.: Clinical Significance of Staphylococci with Natural or Acquired Resistance to Sulfonamides and to Penicillin, J. A. M. A. **128**:555 (June 23) 1945.

There was no evidence that neoarsphenamine was of any value in the therapy of subacute bacterial endocarditis.

Of 12 patients treated with penicillin, 7 (58.3 per cent) have probably been cured. Reports to date would indicate that penicillin may be expected to be efficacious in from 65 to 70 per cent of cases of subacute bacterial endocarditis.

Continuous intravenous administration of penicillin was not satisfactory in the treatment of bacterial endocarditis because of frequent complications.

Continuous intramuscular administration of penicillin was a satisfactory method of treatment.

EDEMA OR HERNIATIONS OF FAT LOBULES AS A CAUSE OF LUMBAR AND GLUTEAL "FIBROSITIS"

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FIBROSITIS as a clinical entity has long been accepted in England, where it constitutes about 12 per cent of all medical cases seen. It has always been recognized, however, that its pathologic foundations are slender, resting as they do almost entirely on the theories of Gowers [1] and the observations, comparatively few in number, of Stockman [2] at the beginning of this century.

We were struck by the high incidence of this disorder amongst a large body of highly selected young men with whom we were in touch, and we made several careful attempts to remove and examine "nodules" which had been palpable to the examining finger through the skin. No areas of fibrosis were ever found, however, in this biopsy material, which in every case included muscle. These negative findings led us to seek a fresh approach to the whole problem, and our preliminary findings were summarized in detail recently.[3] These observations suggested that localized areas of fibrofatty tissue may for some reason, at present unknown, become edematous; and that owing to the unyielding nature of the fibrous investment in which they are enclosed painful tension is set up. It is believed that these observations afford the explanation for the pain in a certain proportion of cases of fibrositis of the back and the gluteal region, and that the pathology has not previously been described because abnormalities of the fibrofatty tissues as a source of pain have not yet received much attention.

It is not claimed that the views put forward here will cover all cases of fibrositis, which is in all probability a composite group. It is hoped, however, that they may lead to an extension of investigation on similar lines.

1. Gowers, W. R.: Lumbago: Its Lessons and Analogues, Brit. M. J. **1:** 117-121 (Jan. 16) 1904.

2. Stockman, R.: Rheumatism and Arthritis, Edinburgh, W. Green & Son, Ltd., 1920.

3. Copeman, W. S. C., and Ackerman, W. L.: "Fibrositis" of the Back, Quart. J. Med. **13:**37-51 (April-July) 1944.

NATURE OF THE PAIN

As the result of the work of Sir Thomas Lewis and his school it has been accepted that the pain of fibrositis generally has its origin in certain focal points from which the subjective pain complained of by the patient is referred according to a segmental scheme. Such referred pain may be felt at a considerable distance from its real source, as is seen in cases of sciatica whose origin may be found in focal points situated in the lumbar or gluteal regions. These points are variously referred to as "trigger points," "myalgic spots," or "fibrositic nodules" when they are palpable. They are definite entities, since it is found that the patient winces involuntarily each time that the palpating finger exerts pressure there, while pressure of the same intensity exerted only a few millimeters distant will not produce the same response; a certain degree of more generalized deep tenderness may however be present and must not be confused. Pain in other areas which is being referred from a trigger point will generally be reproduced by the pressure, in addition to the local tenderness.

The treatment of these points by means of local anesthetic injections is, as is well known, often successful provided that the injection is made sufficiently accurately into the exact spot—not always an easy target.

One of us (W.S.C.C.) has recently observed that the pain in the back which accompanies many of the pyrexial illnesses such as influenza or the exanthems is of the same nature and pattern.[4] Is was shown moreover that, although the pain ceases with the end of pyrexia, in a proportion of cases unknown to the patient the trigger point will persist.

It is thought that this constitutes the basis of some cases of intramuscular fibrositis of the back which may occur at a much later date, when further infection or trauma reactivates the condition.

As will be shown later, these trigger points tend to occur in definite "sites of election" in the lumbar and gluteal regions (fig. 1), and they correspond in the cases to be described, with protrusions of fibrofatty tissue, squeezing of which reproduced the pain, and removal of which relieved the patients of their pain and tenderness.

SITES OF THE PAINFUL SPOTS

Trigger points have been mapped out in a large number of fibrositic patients, and their situation carefully plotted. The result of this in a series of 65 unselected cases is shown in figure 1. This might be termed the "pain pattern."

From above downward the situations in which a majority of these points cluster are: the point where the outer edge of the sacrospinalis

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4. Copeman, W. S. C.: Aetiology of the Fibrositic Nodule: A Clinical Contribution, Brit. M. J. 2:263-267 (Aug. 28) 1943.

muscle meets the posterior costal margin; a spot about 2½ inches (7.4 cm.) above the iliac crest, which is the level at which the latissimus dorsi muscle often crosses the edge of the sacrospinalis muscle; another spot an inch (2.5 cm.) lower, and another at the edge of the sacrospinalis muscle just above the iliac crest. In the gluteal region these points may be found all along the crest of the ilium and for a distance of about 2 inches (5.1 cm.) below it. They may also be found along the sacroiliac junction where the deep fascia is attached. They are much less commonly found elsewhere in the buttock.

ANATOMY OF THE NORMAL BACK

Fourteen backs were dissected with special reference to the areas shown in figure 1, which were the commonest sites for the occurrence of fibrositic trigger points.
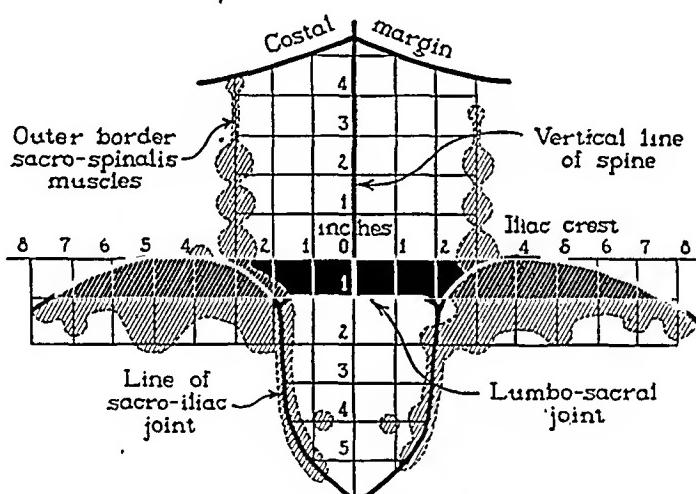
Fig. 1.—The shaded area shows the location of the "trigger points" in 65 consecutive cases of fibrositis.

In the standard textbooks of anatomy not much information can be gained regarding the relationship of the fascial layers of the back with the body fat. The following brief description of our findings seems therefore to be justified.

Deep to the subcutaneous fat and areolar tissue lies a highly vascular sheet of fascia which stretches from the neck to the gluteal region. For most of its area the space between this and the deep fascia is only a potential one, containing little or no fat. In certain well defined places, however, deposits of pinkish fibrofatty tissue occur regularly, and it is these regions, together with the equally constant deep ones to be described, which constitute what we have called the "basic fat pattern" (fig. 2) in view of its constant occurrence even in the most grossly wasted bodies, in which most of the body fat elsewhere had disappeared.

In obese persons this fat pattern tends to become obscured owing to the more generalized deposition of fat.

It was noticed that the fasciae were not of uniform thickness everywhere, being noticeably thinned in certain places, while actual deficiencies were not infrequently found. In these places if fat was lying underneath it tended to bulge through the fascia, and a complete herniation of such fat was sometimes seen.

THE "BASIC FAT PATTERN"

In the lumbar region the sacrospinalis muscle is edged with a strip of fat lying within the angle made by the deep fascia as it splits to enclose this muscle. There is also what may be called the "lumbar fat
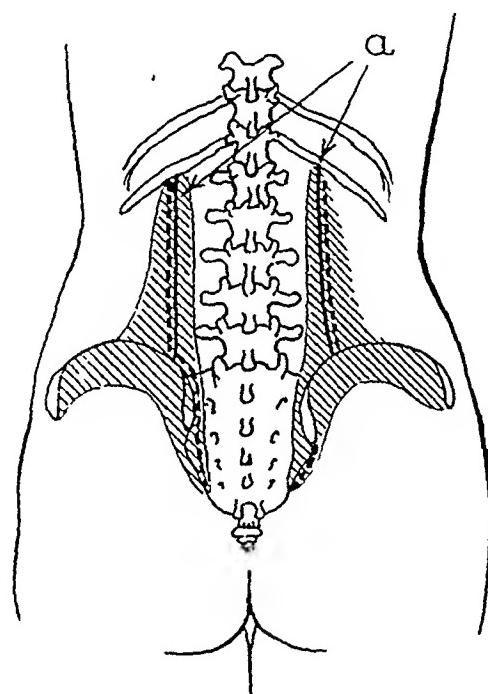
Fig. 2.—The "basic fat pattern." This appears to represent the irreducible minimum of fat in the back under any condition. The dotted lines represent the deeper portion contained in the fascial angle along the outer edge of the sacrospinalis muscle. The letter (*a*) indicates edge of sacrospinalis muscle.

pad," which is a collection of fibrofatty tissue which lies more superficially in the same region. Along the sacroiliac junction there is also a tongue of similar fibrofatty tissue which follows the attachment of the deep fascia and the muscle.

Careful dissection through the lumbar fat pad revealed that it is at the two lower points of maximum tenderness along the edge of the sacrospinalis muscle (fig. 1) that the cutaneous branches of the posterior rami of the last three lumbar nerves pierce the deep fascia, after leaving the body of the muscle. This they appear to do through definite foramens and accompanied by small blood vessels. In 2 of the bodies

dissected a small tuft of fat lobules was protruding through the foramen of the third lumbar nerve in addition to the nerve and blood vessels, probably as the result of postmortem pressure. There is a small horizontal fold of the deep fascia overhanging each foramen, which would seem to be designed to prevent this protrusion of its contents during life by acting as a valve to occlude the foramen on flexion of the back. As the result of the observations recorded later it is believed that these valves do not always perform this function efficiently, and that failure to do so will allow such herniation to occur in the living subject. This may be a cause of sudden acute lumbago which occurs as the result of weight lifting in the stooping position.

In the gluteal region there is a crescent of pinkish fibrofatty tissue which lies along the crest of the ilium and for a distance of about 2 inches below this (fig. 2). It is contained within the layers of the superficial fascia and extends from the anterior superior spine back to the sacroiliac junction, after sending a narrow prolongation down along this region, as shown in figure 2. This lies at a more superficial level than the similar tongue described earlier.

It is not uncommon also to see small "bubbles" along the fascia edging the sacrospinalis muscle, caused by bulging of fat lobules which are contained within the angle of this fascia where it splits to enclose the muscle. These represent weak spots in the fascia, and firm pressure applied immediately adjacent to one of these potential hernias in the cadaver will generally convert it into a fat hernia of the size of a pea or larger.

CLINICAL OBSERVATIONS

To supplement the 10 case histories already recorded,[3] we wish to report here 11 new cases which illustrate the clinical importance of the anatomic observations just discussed.

The therapeutic success which attended the result of the biopsy in every case supports the view that the herniation of fatty tissue through the fibrous fascial compartment in which it was lying was causative of the pain complained of by the patient.

REPORT OF CASES

CASE 1.—*Foraminal Type of Hernia.*—H. H., aged 42 years, had had no serious illness. Fifteen years before (1928) he had an appendectomy under general anesthesia; since then he had had almost continuous backache. This was worse after severe exertion or when he was tired. If he caught influenza or a cold his back became painful during the febrile period. He had had much massage and other physical treatment.

On examination a tender spot was found at the border of the right sacrospinalis muscle 1 inch above the iliac crest. This was transfixed at a depth of 1¼ inches (3.2 cm.). An incision was then made, and the deep fascia was exposed. A small lobule of reddish fat was found to be herniating through a patent nerve foramen at

this point. This was removed—reproducing the pain during the process—and the foramen was enlarged to prevent the possibility of "strangulation" in the event that further fat lobules herniated. The lobule was found to be continuous with the deep basic fat, lying in the angle of the fascia, where it splits to enclose the muscle.

The patient had no subsequent recurrence of pain in this region.

CASE 2.—*Nonpedunculated, Lateral Type of Hernia.*—L. P., aged 30 years, had had severe pain in the left buttock and down the back of the thigh for one year. The original cause was not known. No history of injury or infection was obtained. The pain was most severe when the patient lay in bed. It flared up with an episode of infective hepatitis.

On examination a tender nodule was found in the left buttock. Pressure on this reproduced the pain, which ran down the back of the left thigh to the ankle. All reflexes were normal. Procaine hydrochloride, 10 cc. of a 1 per cent solution, was injected, and the area was "teased" with a thick needle. This definitely improved the condition, but the nodule was still tender and the patient was anxious for permanent cure.

An incision was made over the nodule, and layers of fat in the superficial fascia were cut through. In the second or third layer some tense lobules bulged up into the wound when their septums were cut. One of these, which was the size of a large pea, was removed. The remainder were "teased" and broken up. A definite cavity was left. This fat was superficial to the fascia over the gluteus maximus muscle.

Ten days later the patient was free from pain, and a small hematoma under the scar was aspirated. The pain had not recurred when the patient was seen six weeks later.

CASE 3.—*Nonpedunculated, Lateral Type of Hernia.*—Q. M., 49 years, had had sciatica on the left side for five months. Onset was sudden. The cause was unknown. No history of severe exertion was obtained. It was worse when he lay down in the damp. He had been working hard in his office and thought that he was "run down." Many subcutaneous abscesses developed.

We first saw this patient after he had been in the hospital for ten days for these abscesses. He looked ill and wasted. He had severe pain in the right buttock, radiating down the back of the thigh into the calf and the ankle. Lasègue's sign was strongly positive. Coughing exacerbated the pain. All reflexes were present, and sensation was normal. The roentgenologic examination revealed no bony disease of pelvis or lumbar portion of the spine. There was a definite tender nodule in the left buttock, pressure on which caused pain down the back of the leg to the ankle. Physical treatment and complete rest were employed for three weeks, but the patient still complained of pain and the nodule in the buttock was tender.

A small incision was made into the deepest layer of superficial fascia, and, directly under the site of the maximum tenderness, an edematous fat lobule under tension bulged into the wound. When it was grasped firmly with forceps, but not pulled, it caused the sciatic pain. This lobule was removed, and septal walls were broken down. A large space was left, and hard pressure did not reproduce the pain. He was subsequently free from pain down the leg but had some local soreness of the buttock for two weeks.

CASE 4.—*Deep Nonpedunculated Type of Hernia.*—G. W., aged 32 years, had had backache every winter for five years. In 1943, he was laid up for a week or so with an attack of sciatica on the right side. He was treated in hospital with massage

and rest. Early in December 1943, the pain returned three days after resumption of duty, and persisted in spite of massage and injections into the buttock. Local injection of procaine hydrochloride on readmission reproduced sciatic pain and did not give relief subsequently.

On admission the patient appeared well nourished and had severe pain in the right buttock and down the back of leg into the calf. Lasègue's sign was positive. Definite tender nodules were felt in the right buttock, and pressure on them reproduced the pain down the leg.

Vertical incision was made over the nodule. At first, no abnormality was found. The deep fascia was then exposed and incised, directly under the site of original tenderness. Immediately the patient said, "That's it." A deep compartment containing fat was found to have been opened, and the tense fat, which was the size of a marble, was removed. Septums of fat compartments around this now empty space were broken down by pressure of the finger, and the wound was closed. Next day, the pain had completely disappeared from the buttock and down the thigh. Some pain still remained around the ankle. The patient was encouraged to walk as normally as possible. A week later he still had no pain in the buttock and back of the thigh, but after walking he had a dull uncomfortable feeling in the right ankle, calf and right knee, which lasted for several weeks, but finally disappeared.

CASE 5.—*Nonpedunculated Interseptal Hernia.*—L. B. N., aged 38 years, had had sciatica on the left side for ten weeks. He had been in various hospitals, where he had had injections of nupercaine hydrochloride, sometimes with mild transitory relief. The sciatica was made worse by cold and movement. The pain was severe and shot down the thigh and calf to the heel; it also extended into the left groin. No cause was found. He had had no previous fibrositis or rheumatism.

On examination Lasègue's sign was positive. Some diffuse tenderness was found in the left buttock, and one definite palpable nodule was found, pressure on which caused pain down the thigh. Tender spots were found also at the outer border of the left erector spinae, but no pain was referred from these.

Fat in the superficial fascia of the left buttock was incised. It was extensive, with thick interlobular septums down to gluteal fasciae. The latter looked normal and were not incised. Nothing was at first found until a tense fat lobule, lying directly under the original point of tenderness at a deeper level than had been anticipated, was grasped by the forceps, reproducing immediately the original pain in its whole distribution.

A lobule of edematous-looking fat about the size of a small cherry was removed. No obvious herniation through fascial tissue was discovered.

A week later the patient stated that he had lost all the pain down the thigh as the result of the operation, but that he had still a dull aching pain in the calf. This gradually improved, and a month afterwards he was able to be back at full duty.

CASE 6.—*Pedunculated Fat Hernia.*—A. H., aged 30 years, had suffered for sixteen years with a severe pain in the lower part of the back which had been present ever since he had had a skiing accident and fallen sharply onto that side. The intensity of the pain varied, being worse if he had any mild infection, and in cold weather. He had sometimes to stay in bed on account of it. Physical treatment always made it worse, as did excessive exercise.

A tender nodule was palpated just below the iliac crest and about 4 inches (10.2 cm.) from the midline. An incision was made over this, and a congested-looking lobule of fatty tissue was found lying superficial to the deep fascia, with

a pedicle leading down through the fascia. The pedicle was traced downward and eventually disappeared into the deep layer of fibrofatty tissue which was lying at a deeper level. Two small blood vessels accompanied its course.

Compression of this lobule reproduced the patient's complaint. Hence the lobule was removed. Seen a month later, the patient said that his pain had not recurred and that he considered himself cured.

CASE 7.—*Nonpedunculated Fat Hernia.*—S. M. C. aged 26 years, about four years previously had acquired a severe backache while doing some strenuous exercises. This passed off after a few days with physical treatment. This pain had recurred from time to time, more particularly when he was in poor health. He was seen by us at a time when the pain was particularly bad. A tender nodule could be palpated on the edge of the right sacrospinalis muscle about 1 inch above the iliac crest.

An incision was made with the patient under local anesthesia, and the fat incised down to the level of the border of the muscle. Two "bubbles" of thin fascial tissue were seen at this site, and on incising them a few lobules of fat under considerable tension welled up out of them. On incising the fascia which lay between them it was seen that there was a band of thick fibrous tissue, forming part of the deep fascia, which appeared to have been constricting the base of the fat lobules and so probably accounted for their swelling.

The patient lost his pain as the result of this procedure, and in spite of severe testing it had not reappeared when he was last seen six weeks later.

CASE 8.—*Fat Under Increased Tension, as Result of Old Hematoma, Giving Rise to Pain.*—N. B., aged 33 years, had complained of "lumbago," generally on the left side, for the last two years. Onset was with strain caused by lifting a heavy weight onto his back.

Pain was present most of the time but varied in intensity. When it was bad, the whole back was painful. He had no previous rheumatic complaints. He had had much physical treatment with temporary benefit only.

The patient was heavily built and was of a somewhat plethoric type. A tender palpable nodule was felt towards the midline, opposite the fourth lumbar vertebra. It was about the size of a pea. Surrounding skin was thick and puckered when pinched. Deep pressure reproduced the pain.

An incision was made over the nodule. Subcutaneous fat was divided into compartments by thick fibrous septums. The "nodule" was found to be a tense lobule of fat in such a compartment, and on dividing fibrous tissue it was found to be under considerable tension. A small collection of brownish fluid was also present and was suggestive of an old hemorrhage into the fat lobule.

The cause of the pain here was not herniation, but increased tension in a fat lobule, due probably to trauma in the past.

CASE 9.—*Compression of a Fat Lobule by Deep Fascia.*—Three years ago, P. S., aged 33 years, had pain in the lower part of the spine and the right thigh. Electric treatment and massage were given, and the pain disappeared in a week. Ten months ago the pain recurred after strain. Pain was severe and left him "stooping" for three weeks. For three months he was free from pain, but it recurred when he was lifting a heavy table. Massage and electric treatment gave improvement until two months ago, when pain got severe again and he was readmitted to the hospital. Several injections of procaine hydrochloride gave transient improvement.

On examination pain was severe, and it commenced in the right buttock and traveled down back of the thigh into the calf. It was worse on coughing and on

moving. The patient had difficulty in bending forward at all. Lasègue's sign was positive on the right side. Reflexes were normal. A definite tender spot was found 2½ inches from the midline, and 1½ inch (3.8 cm.) below the iliac crest. Pressure there caused acute pain down the leg.

A vertical incision was made, and fat was found in layers of the superficial fascia, but no definite herniation was encountered. The deep fascia over the gluteus maximus then was incised, with relief of the pain. Beneath this between the digitations of the gluteus muscle were small "fingers" of fat which passed downward through the deep fascia from the superficial fat. It seemed that these were being compressed between this thick fascia and the bone of the sacroiliac ridge. The deep fascia was left gaping, but the fat was not removed.

Two weeks later sciatica had disappeared and had not returned. Some local tenderness was present in the lower fold of the buttock; otherwise the patient felt fit. One month after operation the sciatica had not returned.

CASE 10.—*Nature of Fat Lesion Uncertain.*—S. V., aged 46 years, a well nourished prisoner of war, for three months had had pain in the lower part of the back shooting down the back of the right leg.

On examination there was a definite tender spot over the right edge of the sacrum. Pressure here caused pain down the leg. Less definite tender spots were found in the right buttock also.

A vertical incision was made over the tender point on the right side of the sacrum. The superficial fascia and its contained fat layers were incised down to the fascia over the sacrospinalis. No apparent herniation of fat was noted, but fat in the superficial fascia was thoroughly teased.

Two days later the patient stated that he was cured, for he had no pain whatever on any movement. This prisoner had every reason for not saying that he was cured, as the hospital was more comfortable than the prison camp to which he was discharged. One month later, when the patient was seen in the camp, he still maintained that he was cured, although he stated that he was unhappy there. This was considered proof of the success of the procedure.

CASE 11.—*Fat Hernia of the Direct Nonpedunculated Type.*[5]—S. T., aged 39 years, had no family history of rheumatism and no previous history of any disease other than usual fevers. The onset of pain in the region of the iliac crests was gradual during the last five years but it was most localized and intense on the right side. He had suffered with benign tertian malarial relapses on several occasions during this war, and during these attacks the "lumbago" became much worse. Deep massage at first exacerbated the pain and later generally helped it considerably.

This patient was in the hospital with a malarial attack when we first saw him. He was found to have hard palpable "nodules" on each iliac crest, two of which were exquisitely tender on pressure. Roentgenologic examination of the lumbar spine revealed early osteoarthritis.

An incision was made through the gluteal fat which lay over the tender area. At a depth of about ½ inch (1.3 cm.) a spherical encapsuled "bubble" of tense pinkish fat was found lying under the other fat layers. On palpation it felt hard and reproduced the patient's pain. Squeezing it, without producing tension on its root, caused definite pain. Its removal cured the patient's pain (fig. 3).

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5. Major J. Charnley, F. R. C. S., carried out the operation, and Major F. Brockelbank furnished the photograph.

CLINICAL PATHOLOGY

As the result of biopsies performed on these and other sufferers with "fibrositis" it was found that the trigger points or tender nodules which are characteristic of the disease corresponded in all the cases recorded with herniations or protrusions of edematous fat lobules through deficiencies in the walls of their fibrous compartments.

It was found possible to classify these fat hernias into three anatomic types: (*a*) the pedunculated, (*b*) the nonpedunculated and (*c*) the foraminal types (fig. 4). These names are self explanatory, and a fuller description was previously given.[3]

Microscopic examination of the herniated fat lobules removed at biopsy showed them to consist almost entirely of fat which showed evi-
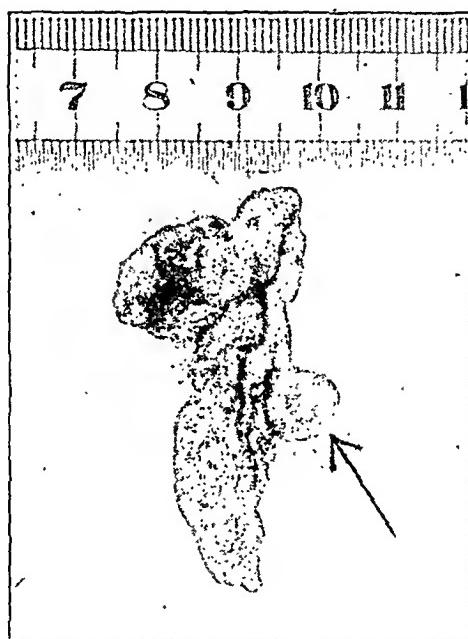
Fig. 3.—Bubble of fat removed in case 11.

dence of edema as its only abnormality. In no case was there evidence of recent inflammatory reaction such as a cellular exudate, although the blood vessels were congested, and in some cases their walls appeared to be thickened. In 3 cases small areas of young cellular fibrous tissue were seen to be growing into the fat, and in the cases of the pedunculated type patches of older fibrous tissue were seen affecting the base of the pedicle, as might be expected.

Owing to the exigencies of active military service we were unable to stain sections for nerve endings.

From the general nature of our approach and as the result of subsequent (unpublished) work it gradually became evident to us that these fat herniations represent a comparatively advanced stage of the disease

process, and that the minor and less localized degrees of pain which are so common as to be almost universally experienced at some time or other may depend on a temporary increase in the fluid tension in the tissues affected, of which the basic cause is so far unknown. When this process has repeated itself sufficiently often, and when the situation is anatomically suitable, actual protrusion of the tissues commences to occur, with the ultimate formation of the herniations which we have described.
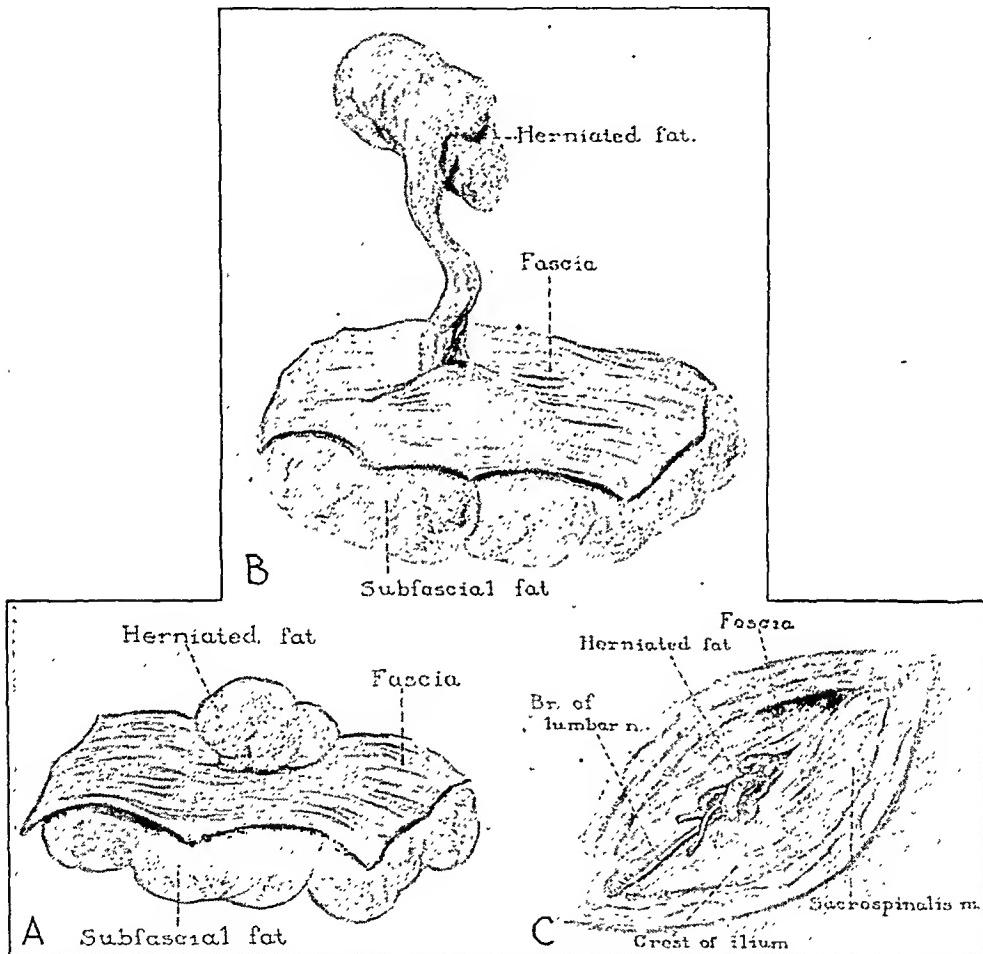
Fig. 4.—*A*, the nonpedunculated type of fat hernia. *B*, the pedunculated type of fat hernia. *C*, the foraminal type of hernia.

PANNICULITIS

As the result of the conclusions which we had reached from our study of the back and the gluteal region it was decided to investigate some cases of that type of fibrositis which occurs around the knee joints chiefly in women who are within the menopausal age zone.

Our observation of this syndrome had suggested that at that period of life fat is normally laid down in this location and that in cases in

which pain developed some abnormality of this fat might be found to be responsible.

We have explored these fatty deposits, when they had become painful, in 6 patients of this type. The fat was found throughout to be divided by firm fibrous septums into small compartments, each containing a few lobules. These took their origin from the subcutaneous region of the skin and passed inward to blend with the deep fascia which invests the vastus internus muscle.

On dividing the walls of these compartments in the painful regions the contained fat lobules immediately bulged out to an extent that suggested that their tension was abnormal. In areas which had not been painful this tension did not appear to be nearly so high.

Careful examination of the affected regions did not reveal any example of herniation of these lobules into neighboring compartments; indeed the walls appeared mostly to be too thick for this to have occurred except with great difficulty.

The therapeutic effect of the division of these fibrous septums over a considerable area was to relieve the patient's pain permanently in 4 cases, while the other 2 reported considerable relief subsequently. Therefore it appears to us that the tension in the fat lobules, which was released as the result of our exploration of the affected regions, might have been associated with the previous pain. It is realized that other explanations could be suggested.

It could not be said with confidence whether the apparent increase of tension in the fat lobules was the result of positive swelling in the fatty tissues, or of contraction of the fibrous elements. However, in view of the variability of the pain, which was affected by such factors as cold or variations in weather, it seemed more probable that the pain was dependent on some variable process such as edema. If this is so, the mechanism already postulated as to the cause of pain in certain cases of fibrositis of the back and gluteal region could also be suggested as being operative in the case of periarticular fibrositis ("panniculitis") of the menopausal type.

THERAPY

The operative procedures in these cases were undertaken chiefly for the purposes of investigation. Although these surgical procedures did cure the patients, we do not advocate them in most cases because we believe that relief can be afforded by other, less drastic measures. We believe that the pathologic conditions described can be shown to have some direct association with several methods of treatment which at present rest on an empiric basis.

Heat, Massage and Movement.—The pathologic basis offered in this paper for the cases of fibrositis described would appear to place these

traditional methods of rheumatic treatment ("the therapeutic tripod") on a scientific footing for the first time. It is reasonable to aim at increasing, by means of heat, the local blood supply and so the drainage from an area which is the seat of gradually increasing congestion, edema and tension.

In the early stages of herniation of the fat lobules, it is equally reasonable to endeavor to "reduce" them by massage, to force the accumulated edema fluid into the lymph drainage channels, and later when they are no longer reducible, owing to adhesions to neighboring lobules, to break them up by mechanical pressure. It seems evident that it is in this way that the disappearance of "fibrous nodules" as the result of massage can be explained.

The rationale of active muscular movement is that it is the essential factor for the efficient functioning of the lymphatic system, and in early cases in which the lesion is still reversible active muscular movement is found to be helpful. It is the common experience that the condition is worse while the patient is lying in bed or after a night's rest.

Injections of Procaine Hydrochloride.—These would seem to be able to act in two ways. In those cases of sudden onset, (e. g., lumbago), which are believed to be due to the sudden herniation of a fat lobule through one of the lumbar nerve foramens or in the basic fat pattern in the superficial fascia, the anesthetic action will relieve the pain for sufficiently long to allow a resumption of muscular movement, which may be sufficient in itself to reduce the protrusion.

More commonly the correct objective of this type of treatment would seem to be to disrupt the fat "nodule" by hydrostatic pressure, and so relieve the local tension on which the pain appears to depend. It is for this reason that such accuracy in making these injections is essential.

"Teasing."—Since we have observed the nature of the "fibrositic" lesion at biopsy, we have evolved a rather different technic, which we refer to as "teasing" the nodule. This process consists in anesthetizing a small area of skin over the site of the trigger point, which has previously been ringed with a skin pencil. The nodule is then transfixed through this area, with a stout rigid "record" needle. After 10 to 20 cc. of 1 per cent solution of procaine hydrochloride is injected under the greatest pressure possible, the cutting point of the needle is swept around deeply in such a way as to "undercut" the nodule, much as a tenotomy knife might be used, in an attempt to divide the pedicle of the herniated portion should there be one and to disrupt also any neighboring lobules which may be sharing in the congestion.

By the use of this method, which must be tempered with at least an elementary knowledge of the anatomic formation of the area being

treated, we have achieved more lasting results than with the normal technic of injection.

SUMMARY AND CONCLUSIONS

A systematic study of fibrositis of the lumbar and gluteal regions has been made in a body of picked men. The pain has been studied clinically, and we have confirmed the occurrence of localized "trigger points" from which pain in this condition may be widely referred. The exact situation in which these occurred in a series of patients was charted, and a "pain pattern" of definite shape resulted.[6]

Our previous observation that these points may arise during any pyrexial illness, or as the result of trauma, was confirmed; also that the subjective pain often disappears, but that the point remains and can be detected by its tenderness on palpation. It can be reactivated subsequently, and may gradually become the seat of chronic pain.

The back was carefully dissected in 14 bodies with particular reference to the sites at which pain had chiefly been found to occur. It was found that a "basic fat pattern" was constantly present, even in the most cachectic subjects, in whom all other fat was absent. This "fat pattern" was observed to correspond with the "pain pattern" already charted, in situation and shape.

Our observations show that the production of pain at these trigger points takes place in certain fibrofatty tissue, and not in the muscles, as has often been stated. The local lesion demonstrated in those cases in which biopsy was performed consisted of an increase in the volume of certain fat lobules in situations where expansion was normally limited by an unyielding fibrous capsule. In one case (case 8) this increased tension in the lobule appeared to be the result of an old hematoma.

In the clinical cases described in this paper this process had progressed further, and actual herniation of these lobules had occurred through weak spots in the fibrous compartment or capsule. The causative nature of these lesions seemed to be confirmed by the patient's freedom from pain subsequent to the removal of the herniations.

Exploration of the painful area in a small series of cases of periarticular fibrositis ("panniculitis") of the menopausal type suggested that a similar mechanism might also be responsible for the pain in these cases.

Physiologic principles underlying certain lines of physical treatment commonly employed in the treatment of fibrositis are shown to be rational for the pathologic conditions described.

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6. Major W. H. Mylechreest, R.A.M.C., provided postmortem facilities and also cut sections of the biopsy material. Dr. Philip Hench of the Mayo Clinic gave assistance and advice in the preparation and presentation of the manuscript.

SCHISTOSOMIASIS JAPONICA WITH CEREBRAL MANIFESTATIONS

Report of Seven Cases

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ABOUT two to three months after the American forces occupied the province of Leyte, in the Philippine Islands, cases of early schistosomiasis japonica were encountered. This report is concerned with a group of unusual complications of this disease. These cases constitute a bizarre picture of an exotic disease, but when they are grouped together a syndrome emerges which can be recognized clinically. Experience in the Far East indicates that in view of the immediate severity as well as the residua of the disease this group is sufficiently important to merit study.

Schistosoma japonicum, like all other trematodes, has a life cycle which includes parasitic infection of an intermediate host prior to the development of the adult worm found in man. The egg, passed from the human or the animal host, quickly hatches a miracidial larva in the fresh water of streams and rice paddies. The free-swimming miracidia seek out a suitable snail of the genus Oncomelania (in these cases). After the miracidia have developed for several weeks in the snail, sporocysts containing cercariae are formed. These are released into the water daily in large numbers. On contact with the skin of man and of other mammals, they quickly penetrate and gain entrance by way of capillaries into the systemic circulation. It is said that only those parasites which arrive in the intrahepatic circulation survive. The majority of worms migrate to the finer radicles of the mesenteric vessels, where they mate and produce ova, but some authors have mentioned the presence of mature worms in the pulmonary vessels. The development of the cercaria into the adult worm requires from five to eight weeks.

A discussion of the relationship of the parasite to the production of symptoms may aid in their recognition. The time of appearance. the character and the site of symptoms vary with the degree of infection. the development (cercaria, mature worm, ova), the toxic or the mechanical effects of the parasite and the reaction of the host.

The cercarial or larval phase lasts a few weeks. Its effects on the skin are immediate, and the reaction may result in localized eruption.

Within two or three weeks after penetration of the skin the filter bed of the pulmonary vascular tree in turn becomes the site where large numbers of young worms exert their effects. A patchy pneumonic involvement may result. So far this stage has not been recognized clinically, since the patients come under observation some time after the pulmonary episode. However, a history suggesting just such an event is frequently given. It is quite possible that this reaction persists for six to twelve weeks after infection, since cough and diffuse pulmonary roentgenographic shadows are present at the time of the initial observation.

The mature fluke deep in the mesenteric radicle probably produces little subjective disturbance, for asymptomatic patients passing ova are encountered occasionally and a long asymptomatic period is noted between the acute and the chronic stage of the disease. Collections of ova in tubercle formation gradually work their way into the intestinal lumen and cause pathologic changes varying from fine scarring to massive distortion of the intestinal structure. The association of symptoms in this process appears clear, and the severity varies with the degree of destruction. In addition to local effects at the site of their production, ova produce far distant involvement through embolic distribution. Ova produced in vascular radicles drained by the portal vein, in addition to penetrating and damaging the liver, may gain entrance to the systemic circulation by way of collateral channels through the hemorrhoidal plexus and eventually reach the lung. The lung becomes the site of multiple areas of ova and their attendant reaction, which occasionally includes small thromboses and necrosis of tissue. Some ova break through and by way of the bronchial artery and pulmonary vein collateral plexus enter the systemic circulation and are swept to distant organs. This mechanism need not be invoked if there is a cardiac septal defect. Day (quoted by Stitt),[1] describing Schistosoma mansoni, stated that rarely adult flukes migrate and are carried to the pulmonary arteries. Although I have no evidence to date that such migration occurs with S. japonicum, as there were no deaths in this series, it must be considered a possible source of metastatic ova. While the means and the pathway of the distribution of ova may not be established, it must be remembered that ova may be found in any organ. It is interesting to note that the scanty bibliography available mentions similar cases in which the disease is attributed to ova deposited in the brain and the spinal cord.

Faust and Meleney[2] stated that Yamagawa, in 1890, mentioned jacksonian epilepsy occurring in a patient with schistosomiasis japonica,

1. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942.

2. Faust, E. C., and Meleney, H. E.: Studies on Schistosomiasis Japonica, Baltimore, American Journal of Hygiene, Monograph Series, 1924, no. 3.

and that Houghton, in 1910, also described a case in which he suspected that symptoms referable to the brain were due to deposits of eggs. They stated that such cases are rare. Spiridion[3] described an outbreak of schistosomiasis japonica in China. Three patients showed neurologic involvement. The first patient was semicomatose and incontinent; bilateral ptosis, flaccid paralysis of the upper limbs and exaggerated reflexes and clonus of the lower limbs were present, while the colloidal gold test showed the curve characteristic of dementia paralytica. The second patient had delirium and coma lasting four weeks, screaming alternating with sleep, trismus, retraction of the head, opisthotonos and Kernig's sign, spasticity of the upper extremities, exaggerated knee jerks and clonus. The spinal fluid contained no cells and the colloidal gold test gave the curve characteristic of dementia paralytica. The third patient presented flaccid paralysis of the left upper and lower extremities, with diminished reflexes. These authors stated that jacksonian epilepsy and hemiplegia had been reported by others. Stitt[1] and Manson[4] mentioned that, in addition to fits, hemiplegia and total blindness may occur after ova have been deposited in the brain.

The cases which I shall report were collected in a hospital functioning and undergoing construction simultaneously during the peak load of the Philippine campaign; it was understaffed and overcrowded, and the laboratory facilities were overburdened. During this time medical care was necessarily and primarily concerned with returning the soldiers to duty. The patients were handled routinely and not in the light of a future report. Only because of the severity of the illness of these patients were notes and laboratory data somewhat more detailed than customary. During this period schistosomiasis assumed epidemic proportions among troops. Six patients with cerebral manifestations were observed among 181 patients with schistosomiasis admitted to the hospital from January 15 to July 15, 1945. An additional patient (case 1) observed at another hospital on the island of Leyte is included.

These soldier patients were aged from 20 to 29. All of them had landed on Leyte for the first time during the interval from "D" Day, Oct. 20, 1944, to Dec. 25, 1944. All of them had been exposed to contaminated water, subsequently proved by survey to contain infected snails. Six soldiers were white, and 1 was Negro. It is not possible to determine whether race played a part in this discrepancy or whether it was a result of the numerical difference of troops. All were healthy and combat fit prior to their illness.

3. Spiridion, J. T.: Schistosomiasis Japonica: An Account of an Outbreak, J. Trop. Med. 39:161, 1936.

4. Manson-Bahr, P.: Manson's Tropical Diseases, ed. 11, London, Cassell & Co., Ltd., 1942.

REPORT OF CASES

CASE 1.—A white soldier was admitted on Jan. 9, 1945, with a diagnosis of encephalitis. He had landed on Leyte, Oct. 20, 1944. He washed and swam in various streams. One of his camp sites had been flooded out early on his arrival. About three weeks before admission he had a "febrile" illness, for which he did not seek medical attention and which he described vaguely. On January 8 he became weak in all his extremities and was sent to the hospital the following day. Examination showed that he was obese, febrile and acutely ill; there was flaccid partial paralysis of both arms and legs with ataxia; all deep and superficial reflexes were present; there were no sensory disturbances; both the great toes and the small toes were discolored and tender. The following day a spinal tap obtained fluid not under increased pressure, containing 12 cells per cubic millimeter; the Pandy test was negative. The abdominal reflexes were absent, and the cremasteric reflexes were just obtained. He became confused, incontinent and restless and answered questions with difficulty. He was unable to focus his eyes and moved his legs incoordinately. Three days after admission, January 12, he had regained some control of the bladder, was disturbed, confused, anxious and complained of painful feet, which were blotchy and purple, particularly the small toes and the plantar aspect. The next day, he was slightly disoriented. Save for loss of convergence, the cranial nerves were intact. The sensorium was intact; there was weakness as well as spasticity of all extremities, with left patellar and ankle clonus. Extension and flexion of the left arm were minimal, and finger extension was absent. The cremasteric reflexes were barely present, there was exaggeration of all deep reflexes with Babinski's reflex positive on the left side and equivocal on the right. The feet were cool, and pulsation of the popliteal and posterior tibial arteries was normal. The total leukocyte count was 27,400, and the eosinophils were 38 per cent. On January 14 the left pupil was dilated, but on January 15 the pupils were normal. The heart and the lungs were normal, the liver was slightly enlarged, firm and not tender, and the spleen was not felt. The patient was less confused. The muscle strength of both arms was 25 per cent of normal, and that of both lower extremities, slightly diminished. The discoloration of the feet was less than it had been forty-eight hours previously; the distal half of the nail of the left index finger also had acquired a bluish discoloration. The hyperreflexia was unchanged; there was sustained patellar and ankle clonus on the left side and nonsustained on the right side; the Babinski reflex was absent. On January 17, additional bluish-discolored lesions were noted on the calves of both legs. The patient was still mentally disturbed. The stools contained ova of S. japonicum. Fuadin therapy (50 cc. of fuadin, containing 0.42 Gm. of antimony) was started and completed on February 4. On January 18 spasticity was less; the pupils were again unequal; confusion and irritation were less, and the temperature, previously ranging between 99 and 100.6 F., became normal. A biopsy specimen taken from the discolored area of the right calf showed skin exhibiting perivascular inflammatory infiltration, vascular changes and thrombosis, with no specific etiologic agent discernible. Two days after therapy, January 19, the patient was clear mentally; the right pupil was dilated in the morning, but at 3 p. m. the pupils were equal and regular and reacted promptly to light. Convergence was still weak. The arms, still spastic, were stronger, but the right forearm was paretic; coordination was poor, and there was sustained patellar clonus, but ankle clonus was transient. Three days after the start of fuadin therapy, January 20, improvement was unmistakable. The patient sat on the side of the bed for a short time. Fluid had

collected under discolored areas of the heels, and the toes had cleared except for the tips, which. were still deeply purple. One week later the muscle power of the arms had increased, and ankle clonus was transient; mild diplopia was present. At the end of the course of fuadin, February 4, an ambulatory status was reached; hand motion was better, but there was still incoordination of the arms, and ankle clonus was not present. Five days later, on February 9, Babinski's reflex and clonus had returned on the left side, and the tips of both small toes were necrotic. These areas gradually became demarcated in the course of the next week, when it was noted, February 15, that his condition was excellent in comparison with what it had been on admission. The following day he was transferred to another hospital.

Summary.—Two to three months after exposure this man suffered from quadriplegia, confusion, disorientation, pupillary changes, paresis of the abducens nerve and incontinence. Recovery was slow and incomplete one and a half months later. Leukocytosis and eosinophilia were evident. Ova of hookworm and S. japonicum were demonstrated.

CASE 2.—A 25 year old Negro soldier was admitted to the hospital on Jan. 24, 1945, complaining of "swelling of the face, the hands and the abdomen."

He had landed on Leyte on Nov. 15, 1944, two months prior to admission. He said that he had not been swimming in fresh water streams but he had washed trucks in the river from December 20 to Dec. 25, 1945, inclusive. He had waded through rice paddies on innumerable occasions. One week before admission he had a cough which lasted for four days and was productive of yellowish phlegm. Three days before admission he suffered from anorexia, weakness, generalized aches and soreness, and both feet felt "dead." Two days before admission an itching eruption developed on the face, the hands, the chest and the abdomen.

Two members of his organization, who worked with him, were in the hospital with schistosomiasis, proved by examinations of the stools.

One aunt of the patient had tuberculosis.

The patient was born in South Carolina. Syphilis and gonorrhea had been contracted three years ago. He had been treated for eighteen months and had several negative serologic tests prior to and after entrance into the Army. Many years previously he had an attack of hives.

Examination disclosed moderate circumscribed edema of the wrist and the flexor surfaces of both arms and slight puffiness of the eyes and of the fingers of both hands. On the lower part of the chest and on the abdomen there were several circumscribed, various-sized, urticaria-like areas. The blood pressure was 110 systolic and 70 diastolic. A diagnosis of angioneurotic edema was made.

The lesions cleared gradually. On January 29, five days after admission, his temperature was 100 F., and he complained of a generalized headache. The headache increased, and aches in the arms and the back, anorexia and frequency and urgency of urination appeared together with a rise of temperature to 102 F. At night he slept soundly and was incontinent of urine and feces. The following morning lethargy and generalized abdominal cramps were present, and it was noted that the deep reflexes were present and normal. That night he climbed out of bed and voided twice on the floor. On February 2, nine days after admission, his condition was unchanged; fever persisted at the same level and the results of neurologic examination were described as negative. For the first time the suspicion arose that this was a case of schistosomiasis. A stool was reported to contain no ova or parasites on February 3. A blood smear was negative

for malaria, and the differential count showed 60 per cent eosinophils. In the next several days lethargy, incontinence, generalized aches and thoracic pains persisted. On February 7 the temperature reached normal. The patient was still disoriented. The liver and the spleen could not be felt. The pupils were small, and the fundi could not be seen. There was spastic quadriplegia with pathologic reflexes, although superficial reflexes were present. The sensory examination was inconclusive. Antimony and potassium tartrate therapy (1.95 Gm. of the compound, containing 0.73 Gm. of antimony) was started February 10 and completed March 12. The patient became ambulatory on his own insistence the day after therapy was begun, and in the next four weeks there was an increase of strength and appetite with a lessening of complaints. At the completion of therapy examination showed the peripheral visual field and the fundus normal, the left patellar and ankle jerks hyperactive, the pathologic reflexes normal and the flexor muscles of the right arm and the left leg still weak. Abdominal distress, cramps in the legs and heaviness were occasionally complained of thereafter until April 28, three months after admission, when a careful detailed examination revealed normal conditions with the exception of a hyperactive Achilles tendon reflex with transient clonus.

The patient was transferred to a center for convalescents.

Summary.—Two months after exposure this man suffered from angioneurotic edema, headache, lethargy, incontinence, change in personality and spastic quadriplegia. Leukocytosis was not present on one examination, although eosinophilia was severe. Ova of S. japonicum were not demonstrated. Two fellow soldiers who had been exposed with him were in the hospital at the same time with proved schistosomiasis.

CASE 3.—A 20 year old white infantryman was admitted to a clearing station on Feb. 2, 1945, complaining of cough and fever of eight days' duration. At the clearing station it was noted that the illness started with an occasionally productive cough, followed by generalized aches.

Fever was present; it was minimal, with the temperature ranging between 99.2 and 100.4 F. by mouth. The patient was thought to have acute bronchitis. Although the cough cleared in a few days, he remained vaguely uncomfortable. Seven days after admission, while he was ambulatory, there was a sudden change in his condition. He became listless, depressed, slightly confused, uncooperative and complained of "feeling bad." The temperature was 100 F. Examination at this time revealed no explanation for the change of condition. Hysteria was considered probable, and he was transferred to the hospital, February 12. On admission the history was sketchy but of some value, and as time went on completion of the history was accomplished.

Arriving on Leyte, Oct. 24, 1944, the patient had been perfectly well until two weeks before he sought medical attention. He swam many times in the rivers of this island, his last exposure being one month before he became ill. Two weeks before he went to the clearing station, a cough developed, which persisted, accompanied with malaise and fever. There were no headaches, visual disturbance, vomiting, eruptions or paresthesia. Two days prior to admission, while in the previous installation, he lost control of his arms, was nervous and was unable to sleep. The left arm rapidly became weak in the two day period. There was no history of swimmer's itch, urticaria or diarrhea. A fellow soldier who had been swimming with him was under observation for schistosomiasis.

Family and personal histories were noncontributory.

Examination disclosed a husky white soldier, who was conscious, listless and lethargic; his response to questions was slow and blocked, and comprehenion was lacking. There was no icterus or eruption of the skin. The pupils reacted normally, and an examination of the fundi revealed nothing abnormal. External ocular movements seemed normal, but cooperation was not secured. The remainder of the examination of the head, the neck, the lungs, the heart and the abdomen gave normal results. The liver and the spleen were not palpable. The cranial nerves were normal; the left upper extremity was not moved voluntarily and was flaccid, and deep reflexes of this extremity were not obtained. The leukocyte count was 23,800, of which 80 per cent were eosinophils. The spinal fluid was clear; it was not under pressure and contained 3 lymphocytes; the globulin was not increased. The urine was normal except for a faint trace of glucose.

The patient spent a restless night and complained of an ache in the left elbow. The following morning he was less drowsy but still listless, reacted to commands slowly and had a peculiar blank stare. The left arm was unchanged; the eyes were normal, and the equivocal Babinski reflex was present bilaterally.

Fuadin therapy (45 cc. of fuadin, containing 0.38 Gm. of antimony) was started on February 14 and completed on March 2. The day after therapy was started a slight improvement in the mental status was present, and simple questions were answered more rapidly. Biceps and triceps reflexes were just present, and there was a slight increase of power in the left arm. In the next three days the patient became alert, moved his left arm voluntarily and talked freely with his fellows. It was noted that although he moved his left arm it was much weaker than the right. There was little change thereafter until the completion of treatment on March 2, when examination disclosed that he was stronger generally and that ataxia of the left hand and clumsiness of the fingers (tying pajamas) were still present. The deep reflexes of the right upper and the left lower extremity were somewhat hyperactive. Sensory examination in all modalities showed normal conditions, and muscle power was apparently normal. Ten days later examination showed that the peripheral fields of vision were normal. There were no outstanding changes thereafter. He was treated on two occasions for hookworm and ascariasis and was transferred to the convalescent section of the hospital. On April 24, eleven and a half weeks after admission, he was well except for some weakness of the left arm—"it felt paralyzed." This condition was especially noticeable when he wrote (left-handed). Examination revealed entirely normal conditions. On May 3, a stool specimen contained S. japonicum.

Summary.—Within three months after exposure this man had cough, malaise and fever, followed by monoplegia, lethargy, blocking and transient involvement of the pyramidal tract affecting the lower extremities. Three months later subjective symptoms were present. Leukocytosis with eosinophilia was observed, and numerous parasites were present in the stool. Ova of S. japonicum were not demonstrated until after convalescence had started.

CASE 4.—A 28 year old white soldier was admitted to a battalion aid station on Jan. 16, 1945, complaining of fever. His temperature was 101 F., and he was thought to have dengue. Three days later slurred speech, incontinence, a bilateral Kernig sign and a left Babinski reflex were present, and he was transferred to an evacuation hospital. Here it was noted that he was lethargic and responded only by shaking his head. On examination there was no nuchal rigidity, and the pupils were equal and regular. The deep reflexes of the upper and the lower extremities were hyperactive; the Babinski reflex, confirmatory reflexes

and ankle clonus were bilaterally present; the abdominal and cremasteric reflexes were absent, and the lower extremities were spastic but not paralyzed. A spinal tap was done; the fluid was clear, was not under increased pressure and contained 6 cells.

The patient was then transferred to a station hospital on January 25. On admission it was noted that a reliable history was unobtainable.

He had arrived in Leyte on Nov. 23, 1944. From that date until the end of November he had gone swimming many times in fresh water streams. Six weeks before admission he had generalized headaches, malaise and fever. He was very hazy in regard to events after that but did not recall "swimmer's itch," hives or cough.

The family history was noncontributory except for paternal hypertension.

Other than for "glands on the left side of the neck" as a child and pneumonia in 1940 he had been in excellent health.

Examination disclosed an acutely ill man who was conscious and answered simple questions hesitatingly and whose frequent exhalations caused fluttering of the lips. His voice was hoarse. He was cachectic and appeared twice his supposed age. Loss of weight was apparent. The left pupil was larger than the right; both reacted to light, and the left lid was slightly ptosed. External ocular movements could not be tested; there was no apparent visual disturbance or deafness. The tongue was dry. The temporal arteries were prominent. There was moderate nuchal rigidity. The heart, the lungs, the abdomen, the genitalia and the articulations were normal. There was no adenopathy. The blood pressure was 104 systolic and 88 diastolic. The right upper extremity was held in constant flexion of the elbow, and the left upper extremity was also spastic; the left lower extremity was flaccid, but some voluntary motion was present. There was a suggestion of weakness of the left seventh nerve. All deep reflexes were hyperactive, and the superficial reflexes were absent. The Babinski reflex, confirmatory reflexes and ankle clonus were present bilaterally. Sensation was intact.

The temperature ranged from 98.6 to 101.6 F. for one week. Semicoma supervened; the pupils became pinpoint in size, and incontinence continued. Three days after admission the liver was palpable 2 fingerbreadths below the costal margin and was extremely tender. Fuadin therapy was started on Jan. 29, 1945 and completed on March 5 (90 cc. of fuadin, containing 0.76 Gm. of antimony). Shortly after therapy was started, he showed signs of improvement, and voluntary movements were increased in the lower extremities. One week later (February 4) he appeared confused, withdrawn and somewhat agitated. Although cerebration was slow and insight lacking he tried to cooperate. He took an interest in his examination for the first time. There was paresis of the lower left side of the face; the left pupil was greater than the right, but both reacted normally. The left side of the palate was weak. Both upper extremities were weak, the left more than the right; the involvement of both lower extremities was less. Bilateral ankle clonus persisted, and the superficial reflexes were still absent. The liver was just palpable and extremely tender. The patient was admitted to the hospital during his fourth week of illness, February 11. He was still unable to give a coherent story. The cranial nerves were intact. Apraxia was present. Simple commands were executed promptly and well, but he had difficulty in choosing words and expressing himself; he was oriented and repeated test phrases. Reflexes were hyperactive with bilateral Babinski reflex and ankle clonus and Oppenheim and Gordon signs on the left side. The blood pressure was 90 systolic and 58 diastolic. The heart and the lungs were normal; the liver was still tender; the spleen was not palpable. In the next two weeks marked progress was made;

control of the bladder was regained, and speech was almost normal. However, simultaneous walking and response to commands were hesitant, unsteady and slow, and he was absentminded. Arthralgia of the large joints was present. The Romberg sign was not present. The fingers were more dextrous. The deep reflexes were greatly increased in the left upper and lower extremities, with associated muscular weakness. Transient left ankle clonus was present, and the superficial reflexes were still absent. Heat and cold sensation were diminished in both legs and feet. The fundi and the peripheral parts of the visual fields were normal. During the next several weeks the patient made good progress. On April 20, seven weeks after the completion of therapy, all his previous disturbances, while present, were less acute. The reflexes were unchanged; the left ankle clonus was sustained; the left upper extremity was moderately weaker than the right, and the left lower extremity was weak, with incomplete foot drop. Shortly afterward he was evacuated to the United States.

Summary.—Two months after exposure this man suffered from diarrhea, headaches, malaise, fever, confusion, aphasia, involvement of cranial nerves, semiconsciousness and paraplegia. After two months there was still residual paralysis. Leukocytosis, eosinophilia and transient roentgenographic pulmonary shadows were present. Ova of S. japonicum were not demonstrated.

CASE 5.—A 27 year old white American soldier was first admitted to another hospital on Feb. 2, 1945, complaining of weakness in walking, pains in the left arm and cough severe enough to prevent sleep. The notes made at that admission are scanty but indicate that he had bathed and swum in rivers on Leyte. One month previously he had been admitted to that hospital for a few days because of fever. The positive findings recorded at that time were mild generalized adenopathy, specifically prominent in the axilla and the groin, obvious instability and ataxia on walking. The temperature was 99.4 F., the pulse rate 80 and the respiratory rate 20. The severity of the pain in the arm required frequently repeated administration of morphine for relief. On admission the leukocyte count was 19,000, with 60 per cent eosinophils. Examination of a stool revealed no ova or parasites. The next day restlessness was disturbing, and the patient would not lie still because of pain in the left shoulder. In the morning he answered questions slowly and was drowsy. There were no signs of meningeal involvement, and the Babinski and confirmatory reflexes were not present.

On February 25 the patient was transferred to this hospital. On arrival he was mute, not responding to questions; he continuously tried to sit up in bed and then would fall to the left. There were constant choreoathetotic movements of the arms and the fingers. Restraints were required.

The following history was taken at a later date: He had been perfectly well until Jan. 8, 1945. He arrived on Leyte, Dec. 25, 1944, and bathed in the streams from that time until Jan. 1, 1945. He noted dull generalized headaches, with occasional sharp scattered head pains and eyeache on January 8; these were constant and prevented sleep. Some time later, severe aching pain began in both shoulders. He continued on duty because of an imminent important military operation. He was hospitalized three to four weeks later because of fever which had been present for an unknown period. At this time he had a cough. He was released from the hospital and was rather vague in his description of what occurred thereafter, but stated, "I must have gone out of my head and was sent to the hospital." He recalled going to the hospital and then was amnesic until seven days after admission to the second hospital. There was no history of "swimmer's itch," urticaria, abdominal pain, vomiting or diarrhea.

The family history was noncontributory. The patient had pleurisy in 1931.

On examination the temperature was 100.4 F. The patient was a dark-complexioned soldier, husky, muscular and in constant motion, rolling to the left. There were no signs of recent trauma. The pupils were equal and small and reacted sluggishly to light. The conjunctivas were clear. External ocular movements could not be tested. A technically difficult examination of the fundi revealed no abnormality. There was slight nuchal rigidity. The lungs were clear except for an occasional transient squeaking rale in the lower lobe of the left lung. The heart was normal, with a rate of 80, and the blood pressure was 130 systolic and 90 diastolic. The liver and the spleen were not palpable. He was conscious but unresponsive. Other than pupillary changes there was no sign of involvement of the cranial nerves. The deep reflexes were hyperactive in the right upper and lower extremities, with equivocal Babinski reflex and sustained ankle clonus; the deep reflexes were absent in the left upper extremity and exaggerated in the lower extremity, with pathologic reflex, and all superficial reflexes were absent. Sensory examination was not possible. A spinal tap (patient struggling) was done. Ten cubic centimeters of crystal clear fluid was obtained, having an initial pressure of 240 mm. of water. There were 22 cells per cubic millimeter (differential count not done); a test for globulin was negative; the glucose content was 87 mg. per hundred cubic centimeters. The leukocyte count on the blood was 16,700, with 78 per cent eosinophils, 10 per cent neutrophils and 12 per cent lymphocytes.

The patient was given sedative treatment, and fuadin therapy was started on February 25 and completed on March 20 (60 cc. of fuadin, containing 0.51 Gm. of antimony). For the next several days there was no apparent change; a low grade fever, with the temperature elevated to 100.4 F., continued, and incontinence persisted. One week later, March 1, he was less confused and spoke monosyllabically. Voiding was frequently voluntary, with periods of retention. When he was urged, he would move his left arm, but otherwise it was not moved. Restlessness prevailed at night. In the following week progress was evident. Examination of the peripheral fields and the fundi during this period revealed no abnormalities. Two weeks later, March 16, he was rational and oriented; speech was slurred; he was unable to repeat test phrases and was extremely clumsy in lighting cigarets; fine movements of the left hand were difficult. The cranial nerves were intact. The left upper extremity was weak, and its reflexes were more hyperactive than those of the right; the reflexes of the right lower extremity were increased, but those of the left were absent. There were no pathologic reflexes except for a transient left clonus; the superficial reflexes were normal and the sensory examination revealed normal conditions. Walking was accomplished with slight difficulty, owing to weakness rather than ataxia; a gain in weight of 10 pounds (4.5 Kg.) was noted on March 27. Four weeks later progress continued, but there was still complaint of weakness of both legs. Although the patient thought that his memory was normal, he was still unable to repeat test phrases. Finer movements were more skilfully performed. There was slight ataxia of the feet. The reflexes of the lower extremities were unchanged; on the left side Babinski's reflex and Oppenheim's sign were still present. Muscular strength was now normal. A few days later, April 3, he was asymptomatic and began convalescent training (consisting of gradually increasing exercise under supervision). When he had his final examination, April 29, he felt weak and his left arm still troubled him occasionally. The deep reflexes in the left arm and leg were hyperactive, but pathologic reflexes were no longer present. The head, the neck, the heart, the lungs, the abdomen and the genitalia were normal. The liver

and the spleen were not palpable, and muscular power was normal. He was evacuated to the United States.

Summary.—About six weeks after exposure this man had cough, fever, malaise, scattered pains, amnesia, aphasia, choreoathetotic movements, incontinence and triplegia. Subjective symptoms and neurologic findings were still present three months after the onset of illness. Leukocytosis and striking eosinophilia were present. Ova of S. japonicum were not found.

CASE 6.—A 23 year old white soldier was first seen at a clearing station on Jan. 30, 1945, complaining of exhaustion. It was noted there that he was vague, uncooperative, disoriented and incontinent. He was transferred to a hospital on February 1. On arrival he was comatose, and a history could not be obtained. Examination disclosed a well developed, well nourished white soldier in coma. He had a pulse rate of 100, a blood pressure of 118 systolic and 70 diastolic, and a respiratory rate of 18. The general attitude appeared at first to be that of catatonia in flexion, but further examination disclosed that there were spasticity and rigidity in flexion, involving both extremities, more marked on the left side. The hands were tightly clenched, with flexion at the wrists and the elbows, the arms being drawn inward so that the fingers rested on the chest at about the manubrium; the legs disclosed only moderate spasticity on flexion, the left more than the right. Movements of the head were resisted in all directions. There was no syndrome of decerebrate or decorticate rigidity, and the optic disks appeared normal. The third, the fourth and the sixth cranial nerves showed inconstant deviation, apparently due to supranuclear involvement. The eyes wandered coordinately at times. There was definite masking of the facies but no definite paresis. The deep reflexes were hyperactive, more so on the left side, with so much spasticity and rigidity that the amplitude of response was limited, and all superficial reflexes were absent. There was too much spasticity in flexion to elicit a Hoffmann sign. The Babinski reflex was bilaterally positive, more so on the left side, and the Chaddock sign was positive on the left side but questionable on the right. The leukocyte count was 16,400, with a differential count of 62 per cent neutrophils, 28 per cent lymphocytes and 10 per cent eosinophils. It was thought that diffuse encephalitis, with probable involvement of the deeper structures, basal ganglions and pyramidal tract was present. The next day, February 2, a blood smear was negative for malaria. The leukocyte count was 23,200, with 45 per cent eosinophils. Clear spinal fluid was obtained, which was under pressure of 16 mm. of mercury, and did not contain cells. The urine was normal. A roentgenogram of the skull revealed nothing. For the next week, February 2 to February 6, there was no evident change. The temperature was elevated to between 102 and 103 F. During this time penicillin, 25,000 units, was given every three hours. On February 3, examination of a stool showed no ova. The total leukocyte count was 19,100, with 40 per cent eosinophils. A second spinal tap showed clear fluid under pressure of 14 mm. of mercury, containing 2 to 3 cells per cubic millimeter.

On the basis of the clinical and the blood picture a tentative diagnosis of schistosomiasis was made, and a course of fuadin was started on February 10 and completed on March 16 (80 cc. of fuadin, containing 0.68 Gm. of antimony). The administration of penicillin was continued for ten days. The patient improved slowly, and the temperature fell by lysis. During this time 3 men from his unit were found to have stools containing S. japonicum. They said that they had been swimming with the patient in Leyte one and a half months ago. On February 12, a specimen of stool contained ova of S. japonicum. By February 14 (four days after the onset of the fuadin therapy) the patient had made remarkable progress.

He was conscious and responded to simple questions in monosyllables or in two or three words. He opened his mouth and protruded his tongue, although slowly and with apparent difficulty. Some comprehension of vision was apparent, but the sensorium was not clear enough or responsive enough for the determination of homonymous defects of visual fields. The spasticity in flexion was still present in the upper extremities, more on the left, so much so that he had excoriated the skin over the manubrial and adjacent areas. Bilateral ankle clonus, Babinski's reflex and Chaddock's sign were present; the masklike facies was persistent, and a mild form of Horner's syndrome was suggested. It was now thought that diffuse encephalitis involving the right hemisphere more than the left and due to S. japonicum was present. On February 25 he was transferred to the hospital where this collection of cases was made. On admission he was disoriented. The history of his illness was obtained weeks later.

He arrived in Leyte, Nov. 23, 1944. During the first week of December he frequently swam in the fresh water streams of this island. About one month later, early in January 1945, chills developed, with pains in the chest—aching in character—and a nonproductive cough (like a cigaret cough). Then pains developed in both upper quadrants of the abdomen, which "came and went," and about the middle of January an urticarial eruption developed; soon fever, frontal headaches and generalized abdominal pains recurred, and he was confined to his quarters. His condition suddenly became worse, and medical attention was sought. He was completely amnesic from then on until he was treated in this hospital.

His family and personal histories were noncontributory.

On admission he was much more agitated than the previous note indicated. He constantly and aimlessly tried to get out of bed; he would crawl to a sitting position, his entire trunk would twist to the right, and he would fall. This happened again and again. Both upper extremities were continuously in athetotic motion. His speech was slow and monosyllabic; the pupils were normal; the mouth could not be examined, and the neck was held stiffly but in rare moments appeared only slightly resistive. There was no adenopathy. The heart and the lungs were normal; the abdomen was voluntarily rigid, so that palpation was valueless, but hepatic tenderness was not present, and neither the liver nor the spleen when percussed seemed enlarged. There was spasticity of all extremities; superficial reflexes were not obtained, there was hyperreflexia throughout, and Babinski's reflex and clonus were bilaterally present. About two weeks after fuadin therapy was begun, four days after admission on March 1, he was apparently clear mentally; ataxia was less, and he understood the use of the urinal. His appetite was ravenous. There was definite improvement; speech now consisted of several words; euphoria was evident, a fatuous grin alternating with a masklike facies. The dystonic movements to the right were less; his reaction to a command was slow, but he answered simple questions slowly, rationally and coherently, in a monotonous voice. He was unable to write; the motions were wasteful, irregular and jerky. Incontinence was no longer present. A nontender liver was palpable 2 fingerbreadths below the costal margin; the cranial nerves were intact, and muscular strength approached normal. All deep reflexes were markedly hyperactive, more so on the right. There was bilateral ankle clonus with a normal plantar reflex; the abdominal reflexes were equal, and the left cremasteric reflex was absent. There were no sensory changes, and he was ataxic only with his eyes closed. There was bilateral apraxia as well as adiadokokinesis. At the conclusion of therapy (five weeks), three weeks after admission to this hospital, he fed himself and carried on long conversations with his neighbors; attendants were

no longer necessary. The peripheral parts of the fields of vision and the fundi were normal, but ataxia and bilateral clonus were still present. In the next few days he had mild discomfort from an infection of the upper part of the respiratory tract. On March 29, two weeks later, he had made further progress. Insight was present; speech was clear. He was mildly agitated and was unable to read because of forgetfulness. There was finger incoordination as well as bilateral intention tremor; ataxia was greater on the left side than on the right; there was no discernible weakness of the spastic lower extremities, and Romberg's sign was not present. He made slow but steady progress, particularly in coordinated movements. On April 24, mild coryza, nausea, anorexia and epigastric soreness developed. Two days later he became icteric and was returned to bed with a diagnosis of infectious hepatitis, then prevalent in Leyte.

Summary.—One to two months after exposure this man suffered from pain in his chest, cough, eruption, fever, headache, amnesia, extrapyramidal tract signs, incontinence and quadriplegia. Two and a half months later residua were still present. Leukocytosis and severe eosinophilia were present. Ova of S. japonicum were demonstrated.

CASE 7.—A 29 year old white soldier surveyor was admitted to a previous hospital installation, Jan. 15, 1945, for hemorrhoidectomy, which was done the following day. On January 21, fever, symptoms of bronchopneumonia, disorientation and confusion were present, and the patient showed motor weakness of the left hand. The next day the leukocyte count was 20,000, with eosinophils 36 per cent, neutrophils 44 per cent and lymphocytes 20 per cent. The urine was normal, and a roentgenogram showed that the chest was normal. The spinal fluid was crystal clear; the leukocyte count was 2, and the Pandy test was negative. Ova of S. japonicum were found in the stool. As a result of these findings the patient was transferred, January 24, to the hospital where this collection of cases was made, with a diagnosis of schistosomiasis with cerebral involvement. On admission the patient was obviously confused and complained of difficulty in thinking and concentration.

He had arrived on Leyte, Oct. 24, 1944. He bathed frequently in local streams and had also waded frequently through rice paddies from Nov. 15, 1944 to Jan. 1, 1945. About five days before he underwent hemorrhoidectomy he had epigastric pain and soreness, which were worse at night and spread to the lower part of his chest bilaterally along the lower ribs; simultaneously hives broke out, which cleared before his admission to the hospital. He had never noticed "swimmer's itch," diarrhea, abdominal pain or anorexia prior to the aforementioned developments. After the operation he became acutely ill, with a temperature of 103 to 104 F.; severe pain in his chest, cough, generalized urticaria, mental confusion and delirium. The fever lasted a few days. After subsidence of the acute phase he noted persistent increasing weakness, insomnia, difficulty in thinking and orientation, confusion and poor memory, numbness in the left arm and in the legs and, later, weakness of the left arm. He had been a printer until two years before admission.

On examination his temperature was 102 F.; the pulse rate was 88, and the respiratory rate was 20. The patient was small, weighing 140 pounds (63.5 Kg.), chronically ill and pale, lying quietly in bed. He was confused, apprehensive and oriented to place only. The head, the neck, the heart, the lungs, the abdomen and the genitalia were normal; the liver and the spleen were not palpable. The blood pressure was 110 systolic and 70 diastolic. There was no adenopathy. The cranial nerves were intact. There was extreme weakness of the left upper

extremity, with hyperreflexia. The deep reflexes of the right upper extremity were normal'; the reflexes were absent in the left and exaggerated in the. right lower extremity. There was bilateral ankle clonus; superficial reflexes were not present. Sensation was normal.

The condition did not change during the next several days. The patient became jumpy and agitated at night; he repeatedly removed his pajamas and then put them on again. He was aphasic in the use of common articles, such as knife, spoon, fork and shaving equipment. Antimony and potassium tartrate therapy was begun on February 1 and completed on March 3 (1.95 Gm. of compound containing 0.73 Gm. of antimony). The day after the start of therapy, vertigo and nystagmus to the left appeared, which lasted three days. He had difficulty in remembering names and in smoking cigarets, and he was unable to write. He was cooperative, alert and coherent, but his speech was slurred. He read and comprehended print. Other than ataxia, adiadokokenesis and slow associated movements on the left side there were no new changes. About five days after the onset of therapy, February 6, he felt better than he had in many weeks; he was more alert and was allowed to walk. For the next two weeks there was a steady return to normal. Transient abdominal distress was present in the left lower quadrant. He was irritable at night. The spleen was palpable for the first time just below the costal margin, and it was noted that although pyramidal tract signs persisted, coordination was better. On March 7, one month after therapy was begun, when he was questioned closely, he admitted that his unsteadiness in walking increased in the dark and that when he concentrated he could give an outward appearance of steadiness but actually felt unsteady. Weakness was less, and memory was excellent. Gain in weight was apparent. The Romberg sign was positive and his gait was slightly ataxic. Involvement of the extremities and ankle clonus were still present, and abdominal reflexes were obtained for the first time. There were adiadokokinesia and apraxia on the left. Fundi and peripheral parts of the visual fields were normal. Ten days later he was able to walk to the mess hall, a distance of 200 yards (182 M.). There was a gradual increase of strength in the ensuing weeks. On the final examination, April 29, he stated that he was unable to concentrate, that his memory was extremely poor (contrary to his previous report) and that he was unable to do automatic acts, such as walking and answering questions simultaneously when addressed—it was necessary for him to stop walking before he spoke or he would fumble his steps. He had gained approximately 10 pounds (4 Kg.). The liver was firm, irregular and palpable 2 fingerbreadths below the costal margin; the spleen was not palpable, and writing was normal. The deep reflexes were still exaggerated, and bilateral suprapatellar clonus had appeared in addition to the ankle clonus. He would constantly overshoot to the left in bringing his finger to the nose. Romberg's sign was now not present; adiadokokinesis and apraxia were still present, and the left upper extremity was weaker than the right.

Summary.—After a two and a half month period of exposure this man suffered from fever, cough, confusion, abdominal pain, urticaria, paresthesias, aphasia and paresis of the left upper extremity and both lower extremities. Residua were present three months after the onset of illness. Leukocytosis and eosinophilia were present. Ova of S. japonicum were demonstrated.

SYMPTOMS

Suspicion of the presence of schistosomiasis should be immediately aroused when there is a history of geographic exposure. The disease is

endemic in the Far East, having been observed in scattered areas of China, particularly the Yangtse Valley, in scattered areas of Japan and in localized areas of the southern Philippine Islands especially Leyte. If there is a history of residence in these areas, careful inquiry should establish specific exposure to contaminated water by drinking, bathing, washing or wading in fresh water streams or rice paddies. The relationship of exposure to the onset of symptoms is important, since in this group acute manifestations began within three months after contact with contaminated water.

A few weeks after contact with contaminated water, malaise, generalized aches, fever, urticaria-like eruption, angioneurotic edema, cough, pain in the chest, abdominal pain and diarrhea may occur. Frequently dengue, malaria, bronchitis, bronchopneumonia or dysentery is diagnosed at this stage even by observers who are cognizant of the disease.

Fever, malaise and generalized aches are not especially characteristic and may be so mild that medical attention is not obtained. Symptoms of involvement of the respiratory tract may appear soon after the fever. First among these is a nonproductive cough; rarely some mucoid material is produced after a paroxysm of coughing. Vague pains and aches occur in the chest which are not related to the cough or the respiration. These pains are mild and fleeting, and the patient may not mention them unless directly interrogated. Hemoptysis is most unusual. Urticarial eruptions, which may appear simultaneously with or follow the fever and the symptoms of involvement of the respiratory tracts, are characterized by their occurrence in a person who does not have an allergic background. The urticaria is generally of the giant type, transient, recurring for several days. Diarrhea is not significant and is difficult to evaluate, since gastrointestinal symptoms are commonly seen in many diseases of this region. Abdominal pain, though important, is rarely severe; while it is frequently generalized, it is more often located in the epigastrium and the right upper quadrant and is described as an "ache" and occasionally as "cramps."

PHYSICAL EXAMINATION

Few specific and characteristic abnormalities are disclosed in physical examination. Fever is variable in degree and duration, but when severe it may be accompanied with late afternoon sweats and chills. Severe cough when present is inadequately explained by the examination of the lungs; rarely, scattered rales and rhonchi are heard, but as a rule the examination reveals nothing pertinent. The liver is tender and palpable. Tenderness is best brought out by indirect heavy percussion, and palpation in the usual manner may not detect it. The eruptions encountered are definitely urticarial; large areas of the skin may be involved, and angioneurotic edema of the lips, the cheeks, the hands and the feet is not unusual.

Table 1.—Laboratory Data in Seven Cases

Date	Hemoglobin, %	Red Cells	White Cells	Eosinophils, %	Urine	Malarial Parasites in Blood Smear	Erythrocyte Sedimentation Rate, Mm. in 1 Hr.	Spinal Fluid	Kahn Test of Blood	Ova or Parasites in Stools	Roentgen Findings
						Case 1. Exposure: 10/20/44 to 12/31/44.					
1/10/45	..	....	....	..	....	......	..	Hospitalized: 1/9/45			
1/11/45	..	....	....	..	Normal	None	..	Normal pressure; 12 cells	....		
1/13/45	..	....	27,400	38	....	....	..				
1/14/45	..	....	39,100	46	....	....	..				
1/17/45	..	....	25,000	54	....	....	..				
1/17/45	(Treatment with fuadin started)							Normal pressure; 3 cells Pandy test negative			
1/23/45	..	....	28,400	61	....	....	..	....	....	Hookworm, S. japonicum	
1/29/45	..	....	....	..	....	....	..	....	....	Hookworm, S. japonicum	
1/31/45	..	....	....	..	....	....	36	....		Hookworm, S. japonicum	
2/ 2/45	..	....	25,000	27	....	....	..	....	....	None	
2/ 4/45	(Treatment with fuadin completed)							....		None	
2/17/45	..	....	....	..	....	....	..	....	....		
2/10/45	..	....	21,000	55	....	....	1	....	—	None	
2/12/45	..	....	18,600	39	....	....	..	....	....	None	
2/17/45	..	....	18,000	40	....	....	..	....	....	Hookworm	
2/20/45	..	....	....	..	....	....	..	....	....	None in many specimens elsewhere	Heart and lungs normal
						Case 2. Exposure: 12/20/44 to 12/25/44.					
2/ 8/45	..	....	....	60	....	None	..	Hospitalized: 1/24/45	....		
2/10/45	(Treatment with antimony and potassium tartrate started)										
2/13/45	..	....	....	..	....	..	..	Normal pressure; cells 0; globulin 0; Kahn test neg.; colloidal gold curve 000 000 000 0	Neg.	None in 15 specimens	

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Table (columns unlabeled on this page fragment; values read left-to-right by date):

Date	Hgb	RBC	WBC	%	Urine	Stool	No.	Spinal fluid	Stool specimens	X-ray / Examination
3/ 5/45										Hazy, indefinite mottling in both lung fields
3/ 8/45						None	8			Lung fields clear
3/ 9/45										
3/12/45			7,400	27	Normal	None				
3/12/45	(Treatment with antimony and potassium tartrate completed)									
4/ 2/45	100	5,000,000								

Case 3. Exposure: 10/24/44 to 12/31/44. Hospitalized: 2/1/45

Date	Hgb	RBC	WBC	%	Urine	Stool	No.	Spinal fluid	Stool specimens	X-ray / Examination
2/ 9/45				70		None		Normal pressure; 3 lymphocytes; glucose 0; globulin 0; Wassermann test neg.; colloidal gold curve 000 000 000 0		
2/12/45		24,600		61						
2/13/45	95	4,600,000			Glucose +				32, specimens; hookworm, A. lumbricoides cysts E. histolytica, sporadically present	
2/14/45	85		23,800	52	Normal					
2/14/45	(Treatment with fuadin started)									
2/16/45	80	3,500,000		82						
3/ 2/45	(Treatment with fuadin completed)									
3/12/45		4,500,000								
4/ 2/45			7,400	10			15		S. japonicum	Heart and lungs normal
5/ 3/45										Skull normal

Case 4. Exposure: 11/23/44 to 11/30/44. Hospitalized: 1/16/45

Date	Hgb	RBC	WBC	%	Urine	Stool	No.	Spinal fluid	Stool specimens	X-ray / Examination
1/16/45								Normal pressure; 6 cells		
1/27/45		4,900,000		17	Normal	None	8		None in 20 specimens	
1/29/45			21,200							
1/30/45	(Treatment with fuadin started)							Normal pressure; 13 cells (lymphocytes 10, polymorphonuclears 3); globulin 0; glucose 65 mg. per 100 cc.; Kahn test neg.; colloidal gold curve 000 000 000 0; sterile		
2/ 2/45	90	5,100,000	12,600	29						
2/ 5/45	90	5,200,000	15,900	41	Normal					

TABLE 1.—Laboratory Data in Seven Cases—Continued

Date	Blood Count Hemo-globin, %	Red Cells	White Cells	Eosino-phils, %	Urine	Malarial Parasites in Blood Smear	Erythro-cyte Sedimen-tation Rate, Mm. in 1 Hr.	Spinal Fluid	Kahn Test of Blood	Ova or Parasites in Stools	Roentgen Findings
Case 4. Exposure 11/23/44 to 11/30/44. Hospitalized: 1/10/45—Continued											
2/ 6/45	90	5,200,000	......	..			..		.....	....	Indefinite hazy mottling of lungs
2/15/45	..	....	......		....	......		....	.....	....	
2/25/45	90	4,900,000	9,800	16			..		.....	....	
3/ 5/45	(Treatment with fuadin completed)										
3/ 6/45	..	....	......	..	....	......		....	.....	....	
3/ 8/45	90	4,000,000	9,500	11	Normal	......		....	.....	....	Shadows un-changed; skull normal
3/10/45	..	....	......	..	Normal	......	11	....	Neg.	....	
3/22/45	..	....	......	..	Normal	......		....	.....	....	Upper lung fields clear
3/20/45	..	....	13,700	6		......		....	.....	....	Lungs clear ex-cept for hazy mottling at left base
4/23/45	90	....	16,300	16		......	..	....	.....	....	
Case 5. Exposure: 12/25/44 to 1/1/45. Hospitalized: 2/2/45.											
2/ 2/45	..	....	19,000	60	....	None	..	....	.....	None in 20 speci-mens	
2/23/45	..	....	19,000	60	....	None	..	....	.....		
2/25/45	..	....	16,700	78	Normal	None	..	Pressure (struggling) 240 mm. water, 22 cells glucose 87 mg. per 100 cc.; globulin 0	.....		
2/25/45	(Treatment with fuadin started)										
3/ 2/45	..	....	......	..	....	......	..	....	.....	....	
3/ 3/45	95	4,500,000	......	..	....	......	..	....	.....	....	Heart and lungs normal
3/ 7/45	..	....	......	..	....	......	..	....	.....	....	
3/ 9/45	..	....	......	..	....	......	..	....	Pos.	....	
3/15/45	..	....	......	..	....	......	..	....	Neg.	....	Skull normal

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Date									
3/19/45	95	5,100,000	13,400	44	None	....	....	.....	Skull normal
		(Treatment with fuadin completed)							
3/20/45	..	....	15,900	27	None	....	....	.....	
3/27/45	..	....	10,900	18	None	....	....	.....	None
4/11/45	..			7					

Case 6. Exposure: 12/1/44 to 12/7/45. Hospitalized: 1/30/45

Date									
2/ 1/45	..	....	16,400	10	.....	Normal	Clear; pressure 16 mm. Hg; cells 0	.....	....
2/ 2/45	..	....	23,200	45	None	....	....	.....	None
2/ 3/45	..	....	10,100	40	None	....	....	.....	
2/ 6/45	90	4,000,000	19,000	40	None	Normal	Clear; pressure 14 mm. Hg; cells 5	.....	Lungs clear; heart normal
2/ 8/45	..	....	.....	45			.	.....	
		(Treatment with fuadin started)							
2/10/45	..								S. japonicum Repeated speci- mens thereafter negative (15-20)
2/12/45	..	....	.....	..	.....	....	....	.....	
2/14/45	..	....	17,500	30	None	Normal			
2/27/45	..	5,400,000	12,600	20	None	....	....	.....	
3/ 1/45	..	....	.....	..	.....	....			
3/13/45	..	....	8,800	12	None	....	....	1	
3/14/45	..	....	6,300	3	None	....			
		(Treatment with fuadin completed)							
3/27/45	..	....	10,000	0	.....	Normal			
4/25/45	90	4,500,000	10,400	6	None	....			

Case 7. Exposure: 11/15/44 to 1/1/45. Hospitalized: 1/15/45

Date									
1/ 0/45	..	....	......	..	.....	....	....	.....	....
1/21/45	..	....	......	..	.....	....	....	.....	....
1/22/45	..	2,200,000	20,000	36	None	Normal	Clear; cells 2; Pandy test negative	.....	S. japonieum
		(Treatment with antimony and potassium tartrate started)							
2/ 1/45	..	....	......						
3/ 3/45	..	....	......	..	.....	Normal	Clear; cells 2; Pandy test negative colloidal gold curve 111 110 000 0	Neg.	Thereafter none in 15 to 20 specimens
		(Treatment with antimony and potassium tartrate completed)							
3/ 3/45	90	3,300,000	10,000	14	.....	....	....	.....	....
3/ 9/45	95	4,600,000	......	..	.....	....	....	.....	
3/11/45	..								Chest normal
3/18/45	..		7,000	6	None			.....	Chest normal
3/26/45	..		6,700	6	None			.....	Chest normal
4/20/45	..		7,300	10	None			.....	Skull normal

TABLE 2.—Summary of Case Reports

Case	Landed on Leyte	Exposure	Hospitalized	Prodromal Symptoms	Time Before Cerebral Manifestations	Cerebral Manifestations	Blood Count on Admission		Ova or Parasites in Stool
							White Cells	Eosinophils, %	
1	10/20/44	Oct.-Dec.	1/9/45	"Fever"	3 weeks	Confusion, disorientation, involvement of cranial nerves, quadriplegia, normal sensation	27,400	38	S. japonicum, hookworm
2	11/15/44	12/20/44 to 12/25/44	1/24/45	Cough, weakness, anorexia, aches, angioneurotic edema	2 weeks	Headache, lethargy, change in personality, incontinence, quadriplegia, normal sensation	?	60	None
3	10/24/44	Oct.-Dec.	2/1/45	Cough, malaise, fever, "acute bronchitis"	3 weeks	Confusion, monoplegia, lethargy, transient spastic paraplegia, normal sensation	24,000	61	Hookworm, A. lumbricoides, E. histolytica, S. japonicum
4	11/23/44	11/23/44 to 11/30/44	1/16/45	Headaches, malaise, fever, diarrhea, "dengue"	2 weeks	Confusion, aphasia, involvement of cranial nerves, quadriplegia, questionable sensory disturbance	21,200	17	None
5	12/25/44	12/25/44 to 1/1/45	2/2/45	Fever, headache, cough	3-4 weeks	Amnesia, aplasia, choreoathetotic movements, incontinence, triplegia, normal sensation	19,000	60	None
6	11/23/44	12/1/44 to 12/7/44	1/30/45	Chills, pain in chest, productive cough, rash, headache, abdominal pain	3-4 weeks	Headache, amnesia, extrapyramidal tract signs, incontinence, quadriplegia, normal sensation	16,500	10	S. japonicum
7	10/24/44	11/15/44 to 1/1/45	1/15/45 for operation	Epigastric pain, hives, pain in chest	11 days	Insomnia, confusion, aphasia, triplegia, normal sensation	20,000	35	S. japonicum

The patients with cerebral involvement presented these characteristics of schistosomiasis in addition to the signs and symptoms resulting from the specific localization of ova: All patients were hospitalized because of the severity of symptoms within thirty-nine to a hundred days from the day of their first possible exposure (eighty-one, seventy, one hundred, fifty-four, thirty-nine, sixty-eight and eighty-three days). All had prodromal symptoms, which varied in severity and were not identical in all patients. In order of frequency the symptoms were as follows: fever, 4 patients; cough, 4 patients; weakness and malaise, 3 patients; urticarial eruption, 3 patients; headache, 3 patients; abdominal pain, 2 patients; pain in the chest, chill and diarrhea, 1 patient, respectively. Symptoms were almost always multiple in each patient. In every instance there was a lucid interval of eleven to twenty-eight days between these symptoms and the onset of neurologic disturbances. Usually the change from the prodromal to the cerebral phase was insidious, but occasionally it was abrupt.

Aphasia, amnesia, blocking, confusion, disorientation, defective memory and coma were outstanding. Spasticity, occasionally early flaccidity changing to spasticity, rigidity, hyperreflexia, pathologic reflexes and loss of superficial reflexes were common to all. In cases 1, 2, 4, 5 and 7 transient disturbances of the third, the fourth and the sixth cranial nerves were present, and in cases 6 and 7 there was questionable involvement of the facial nerve. Although motor paralysis was characteristic and involved one or more limbs, a lower motor neuron lesion did not occur in any of the patients. Sensation was not affected in any case, with the possible exception of case 4.

LABORATORY FINDINGS

The laboratory findings of schistosomiasis will be discussed both generally and specifically in relation to the neurologic disturbances.

During the period when the patients were under my observation, the first four to six months of the disease, the hemoglobin content of the blood and the erythrocyte count did not seem affected. Rarely a mild to moderate decrease of both the hemoglobin value and the red blood cell count was seen, for which another cause was generally present (malaria, malnutrition, multiple parasites). The anemia responded equally well to the administration of iron and to the therapy of the associated complication. Neither fuadin nor antimony and potassium tartrate exerted an effect on the blood count, and at the end of therapy both the hemoglobin and the erythrocytes were within the normal range.

The total leukocyte count and the eosinophil percentage were always elevated. The leukocyte count varied between 10,000 and 50,000; the eosinophil percentage also varied and within the first four months of exposure reached 40 or higher. A finding considered characteristic was

the progressive increase of eosinophilia within the first two weeks of hospitalization (cases 1, 4, 5 and 6). The neutrophil and lymphocyte percentages were not significant. Platelet determinations were not made. The significance of change in the sedimentation rate was not clear; the rate was moderately elevated in only half the cases and was generally normal at the conclusion of therapy. Frequently (incidence not determined) the roentgenogram of the chest showed changes. These consisted of soft, indefinite, hazy mottled shadows symmetrically distributed throughout both pulmonary fields, closely simulating the lesions of miliary tuberculosis but differing slightly in that they were larger, less profuse and not so sharply demarcated. At times bronchopneumonia was present, the lesions being restricted to the lower lobes. The changes lasted from two to four weeks. The effect of therapy on the disappearance of shadows could not be evaluated, as all patients whose disease was diagnosed were treated and there were no controls.

According to Johnson and Berry,[5] proctoscopic examination in 67 per cent of 63 cases showed characteristic yellow tubercles containing ova. Occasionally these were seen before ova were demonstrated in the stool. This has also been my experience, although tubercles were not seen in the patients whose stool contained no ova.

The stool was examined by many technics; the concentration method was thought to give the highest yield of positive results. While the presence of ova establishes the diagnosis, they may be extremely difficult to find, as the following history obtained from the surgical service illustrates.

A Filipino guerilla aged 24 was operated on because of a gunshot wound of the abdomen. The liver and the spleen were not large. The sigmoid flexure and the bladder were perforated in several places, and portions of the epiploic appendixes were lying free in the abdominal cavity. These when studied histologically revealed encysted ova of S. japonicum and portions of the adult worm. Stools were obtained through a colostomy wound twice daily for two days and then daily for eight days before ova were recovered from the twelfth stool. During this time hookworm ova were frequently found.

In addition to the results of the previously described laboratory procedures, those of 11 spinal fluid determinations are available in the reported cases. With the exception of a questionable elevation of the cell count in 3 cases, all results were within normal limits. The spinal fluid pressure was normal in 5 patients and elevated in 2 struggling patients. The cell count ranged from 6 to 22, including both lymphocytes and leukocytes, and was below 6 in eight specimens. The globulin was within normal limits in 4 cases. Quantitative determinations of glucose on two occasions gave 65 and 87 mg. per hundred cubic centimeters.

5. Berry, M. G., and Johnson, A. S., Jr.: Schistosomiasis, to be published.

DIAGNOSIS

When hundreds of cases appeared, it became evident that the clinical syndrome was so clearcut as to permit diagnosis in the absence of a stool containing ova. Although it was realized that a nonconfirmed clinical diagnosis was not a preferable procedure, the importance of starting therapy in an early stage of the infection outweighed the possible harm resulting from the occasional diagnostic error. As time went on justification for this point of view resulted when ova were recovered either during or long after therapy in many patients treated because of a clinical diagnosis and in the absence of rectal tubercles or characteristic ova. Case 3 is a typical example. Here a diagnosis was made clinically, and therapy was instituted. Although numerous examinations (thirty-two) of the stool had revealed no ova during three months' observation, ova were finally encountered shortly before the patients' discharge, and thus the diagnosis was confirmed. It was considered that cases 2, 4 and 5 fell into this category, and they therefore were included in this series.

Schistosomiasis can be suspected when, after the patient has been exposed to the parasite, the following appear: urticarial eruption (in a previously nonallergic subject), pulmonary symptoms, vague gastrointestinal aches, a leukocyte count over 15,000 and an eosinophil count which either exceeds 40 per cent or is shown to rise to that level by serial counts within a short period. Cerebral involvement is indicated when the neurologic signs and symptoms described appear.

When cases occur in epidemic proportion, making a diagnosis is relatively easy. In isolated instances, however, schistosomiasis with cerebral complications may be mistaken for any generalized disease in which there are cerebral involvement and severe eosinophilia.

The conditions from which schistosomiasis must be distinguished can be divided into three groups: (1) other parasitic infections: Ascaris lumbricoides, Ancylostoma or hookworm, Strongyloides stercoralis, Trichinella spiralis, Filaria; (2) neurologic disease in association with other parasitic infections, such as epidemic encephalitis and hookworm; (3) other diseases, such as allergic disorders, periarteritis nodosa, Hodgkin's disease of the skin, Loeffler's syndrome and myelogenous leukemia.

Acute hyperinfection with A. lumbricoides, hookworm or S. stercoralis may produce urticaria and pulmonary, gastrointestinal and cerebral symptoms, with severe eosinophilia, and, conceivably, at an early stage may not be distinguishable from the disease produced by S. japonicum. This difficulty of differentiation must be extremely rare and more applicable to children. During the period when schistosomiasis was rampant the hospital cared for 105 patients with A. lumbricoides, 276 with hookworm and 31 with S. stercorales, these patients presenting both single and multiple infections. The great majority of these infec-

tions were necessarily acute and of short duration. The symptoms were mild and not to be compared with those seen in the patients with schistosomiasis. Minor gastrointestinal complaints, abdominal discomfort, diarrhea and inconstant moderate eosinophilia (the count being rarely above 30 per cent) were common to the group. In only 1 patient was atypical pneumonitis encountered which might have resulted from infection with A. lumbricoides. A few cases of severe hookworm infection occurred among medical personnel at another hospital on Leyte. The outstanding features of this syndrome were fever, diarrhea, severe ulcerlike pain that was increased at night, was not relieved by an ulcer regimen and required morphine, acute anemia and marked eosinophilia. The character of the pain and the severe anemia distinguished ancylostomiasis from schistosomiasis. Severe strongyloidiasis is accompanied with severe watery diarrhea, abdominal pain and loss of weight. Ova of A. lumbricoides and hookworm and motile larvae of S. stercoralis are readily found in the stool, although occasionally they may be difficult to recover. If the cause of severe cerebral involvement is still in doubt and parasitic invasion is presumed, therapeutic trial may be most helpful. Migrating larvae will not be affected whereas there will be a definite response in schistosomiasis.

In recent years attention has been called to the association of severe eosinophilia and filariasis. Reports have appeared from widely scattered regions in the tropics, so that the syndrome due to this infection must be considered in a discussion of schistosomiasis. It is characterized by generalized lymphadenopathy, hard splenomegaly, protracted nocturnal asthma and occasionally acute nephritis.

Trichinosis may resemble schistosomiasis. The history of pork consumption, the severe muscular aches and tenderness, especially of the gastrocnemius and deltoid muscles, the conjunctival hemorrhages, the conjunctival and scleral edema, the results of a biopsy of muscle, and the negative results of examination of the stool and of proctoscopic examination should distinguish the two.

Neurologic disease in the presence of parasitic infection, excluding encephalitis, furnishes little difficulty in diagnosis. The negative results of examinations of spinal fluid in my cases are in sharp contrast with the increase of spinal fluid pressure and of cell count, globulin and glucose seen in cases of encephalitis. The tender, slightly enlarged liver, the more pronounced eosinophilia and the greater frequency of urticarial eruption in cases of schistosomiasis also aid in differentiation.

In the presence of allergic disorders the familial and personal backgrounds are helpful. Frequently a history of a similar occurrence is obtained. The chronologic order of symptoms following exposure is lacking; fever and a tender liver are not common, and eosinophilia is less severe.

The remaining group of diseases can be distinguished from schistosomiasis by a careful study of the history, particularly that of exposure followed by the typical progression of symptoms; cardiac and renal involvements are unusual in schistosomiasis, and adenopathy is absent. The laboratory findings when positive are diagnostic.

<div style="text-align:center">THERAPY</div>

The therapy of this disease, as a result of the experience on Leyte and the follow-up studies in the United States, is in a state of flux. The treatment employed in the cases reported by me should not be considered ideal. Intramuscular injection of fuadin and intravenous injection of antimony and potassium tartrate were both used. Fuadin was given originally in a series of injections totaling 45 cc. of fuadin (0.36 Gm. of antimony) over a period of seventeen days. Reactions were negligible. Electrocardiographic changes were minimal in contrast with the changes induced by antimony and potassium tartrate. They appeared in less than 50 per cent of the cases after 35 cc. of the drug had been given. Later the dose was increased, because ova had been found to be present after the therapy. Antimony and potassium tartrate in a 1 per cent solution was employed in a series of fifteen intravenous injections over a period of twenty-nine days (0.73 Gm. of antimony). The solution was prepared daily and injected slowly without further dilution. Reactions consisting of severe cough, pain in the chest, vomiting and mild to moderate collapse were frequent and occasionally so severe as to induce a change to fuadin. Although symptomatically and in physical examination evidences of cardiac damages were not forthcoming, the electrocardiogram showed considerable change in nearly every case. Low voltage and inversion of T waves in several leads were prominent, but arrhythmias were not seen. The changes became manifest after 9 cc. of the solution (0.066 Gm. of antimony) had been given and frequently persisted for two and three months. It should be emphasized that in spite of these disturbing electrocardiographic changes subjective discomfort and evidences of cardiac involvement were not present clinically.

A review of the case reports indicates that the effects of both fuadin and antimony and potassium tartrate were beneficial. Improvement in the condition of all patients was noted at the conclusion of treatment. This short period of observation indicated that the amount of antimony given did not eradicate the parasite in all cases (case 3). One must conclude that prolonged observation is necessary for the determination of a cure and that an increase of the dose of the drug beyond that which was employed is indicated.

<div style="text-align:center">COMMENT</div>

Residua involving the pyramidal and extrapyramidal tract and the cortex were present three months after the onset of disturbances of the

central nervous system. How long these defects will persist and how permanent they will be can be answered only by future study. Will scar formation and progressive fibrosis produce permanent secondary involvement?

There are two sources from which cases identical with those reported may arise in the United States: first, a group in which the disease may result from rapid air transportation from endemic areas and, second, a group in which the disease has been asymptomatic, undiagnosed or not entirely cured by treatment.

CONCLUSION

Schistosomiasis should be considered in obscure diagnostic problems, including neurologic disease suggesting encephalitis or multiple sclerosis, if the patient is a soldier who has returned to the United States from an area in which it is endemic.

Lieutenant Colonel M. G. Berry and Major A. S. Johnson supplied the data of case 1.

Colonel Henry M. Thomas Jr. helped in the preparation of this report.

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TESTS OF LIVER FUNCTION IN SCHISTOSOMIASIS JAPONICA

With Particular Reference to Antimony Treatment and
With Report of Two Autopsies

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I T IS WELL known that repeated infection with schistosomiasis japonica may result in cirrhosis of the liver.[1] American soldiers who contracted this disease on the island of Leyte in the Philippines during the fall and winter of 1944 had but limited exposure to the cercariae of Schistosoma japonicum, so that their ultimate prognosis may be quite different.[2] During a serial study of tests of hepatic function in a group of 481 such patients, 2 died as a result of external violence about seven months after the onset of the disease, and their hepatic lesions were studied at autopsy, both grossly and microscopically. The observations on the hepatic lesions together with the results of tests of hepatic function done in relation to treatment in the whole group form the basis of this report.

REPORT OF CASES

CASE 1.—*Clinical.*—This 23 year old patient was exposed to the cercariae of Schistosoma japonicum in an endemic area sometime during a period of approximately ten weeks. He first had symptoms compatible with a clinical diagnosis of schistosomiasis at about the eighth week of this period, but ova of Schistosoma japonicum were not identified in his stools until ten weeks later. During the next three weeks he received 13.5 cc. of fuadin. Stools then became free of ova, but the exact time with reference to therapy is not known. Three weeks after completion of the course of fuadin the patient was seen in this hospital. The physical examination at that time showed no significant abnormality except for slight tenderness on deep palpation under the right costal margin. The patient com-

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1. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942, p. 1429.

2. Mason, P. K.; Daniels, W. B.; Paddock, F. K., and Gordon, H. H.: The Latent Phase of Schistosomiasis· Japonica, to be published.

plained of mild epigastric discomfort and slight generalized weakness. Eighteen per cent of the white blood cells were eosinophils. All tests of hepatic function were normal in result except one, which was repeated later and found to be normal. The tests and their values were: icterus index, 6; serum bilirubin, 0.3 mg. per hundred cubic centimeters; serum globulin, 2.9 Gm. per hundred cubic centimeters; cephalin flocculation, negative; bromsulfalein, 4 per cent, and the intravenous test for hippuric acid, 1.23 Gm. The value for the galactose tolerance test was 4.49 Gm., but when the test was repeated two months later the value was 2.49 Gm. A cutaneous test with Schistosoma mansoni antigen elicited a positive reaction. Five successive stool examinations beginning three weeks after completion of treatment with fuadin gave negative results, but six weeks later in a series of 6 more examinations of stools eggs of Schistosoma japonicum were identified. Treatment was begun with antimony and potassium tartrate, and at the time that the patient was accidentally killed by an automobile he had received eight doses or 152 cc. of a 0.5 per cent freshly prepared solution

Fig. 1 (case 1).—Cut section of liver, showing largest nodule.

(antimony, 0.274 Gm.). Death occurred about seven months after the onset of the disease.

Autopsy.—A complete autopsy was performed. The cause of death was readily determined as being multiple fractures of the skull with laceration of the brain. Interest, however, centered in the lesions referable to schistosomiasis which were demonstrable in the jejunum, ileum, ascending, transverse and descending colon, and liver, all other viscera being normal. When the gastrointestinal tract was slit open numerous whitish yellow nodules of about pinhead size were found in the mucosa from the jejunum through the descending colon. In the ileum 35 and 40 cm. from the ileocecal valve there were two oval areas 3 by 1 cm. with depressed centers and rolled margins but with no frankly gross ulceration. The liver weighed 1,600 Gm. It was pale reddish brown and smooth except for a sprinkling of yellowish white nodules up to 0.3 cm. in diameter. On cut section similar nodules were found throughout. An example of the largest nodule is shown in figure 1.

Microscopic examination of the intestines and the liver showed two types of lesions: minute frank abscesses and pseudotubercle formations. Figure 2 shows a photomicrograph of a section through the transverse colon. The mucosa contains many leukocytes and lymphocytes but is not ulcerated. In the submucosa a typical abscess is seen. Centrally it is composed of degenerating leukocytes surrounding which there is a loosely woven fibroblastic network with heavy cellular deposition containing eosinophils, lymphocytes and plasma cells. Adjacent to the abscess is a pseudotubercle formation. It is of interest that within as small an area as one low power field the initial and presumably final
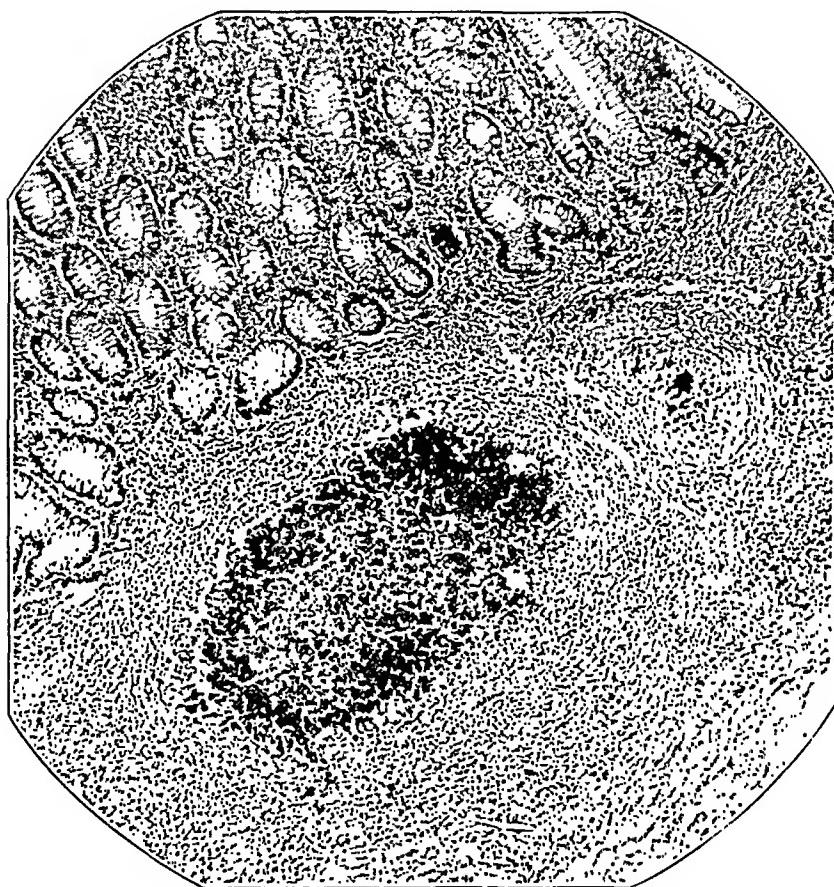
Fig. 2 (case 1).—Photomicrograph of a section through the transverse colon. × 400.

tissue response to an egg are seen. Figure 3 shows a photomicrograph of a submucosal pseudotubercle in which a distorted egg is clearly seen in the upper right portion. The hepatic lesions are similar to those described in the next case.

CASE 2.—*Clinical.*—This 21 year old patient with schizophrenia committed suicide. He had been on Leyte where it was believed that he had contracted schistosomiasis japonica in December 1944. The diagnosis was established on a basis of clinical findings together with positive identification of Schistosoma japonicum eggs in the stool. Fuadin, 45 cc. (antimony, 0.392 Gm.), was given in a sixteen day period. Approximately six months later the patient was examined

in this hospital, at which time he did not have a palpable liver or spleen but did have tenderness along the right costal margin. There were no gastrointestinal complaints. A long blowing diastolic murmur was heard to the left of the sternum and systolic and diastolic murmurs over the apex (rheumatic endocarditis, old). The laboratory data showed that five successive stools were examined by direct smear, sedimentation, egg-hatching and zinc sulfate technics and were negative. A single specimen from sigmoidoscopy was also negative.
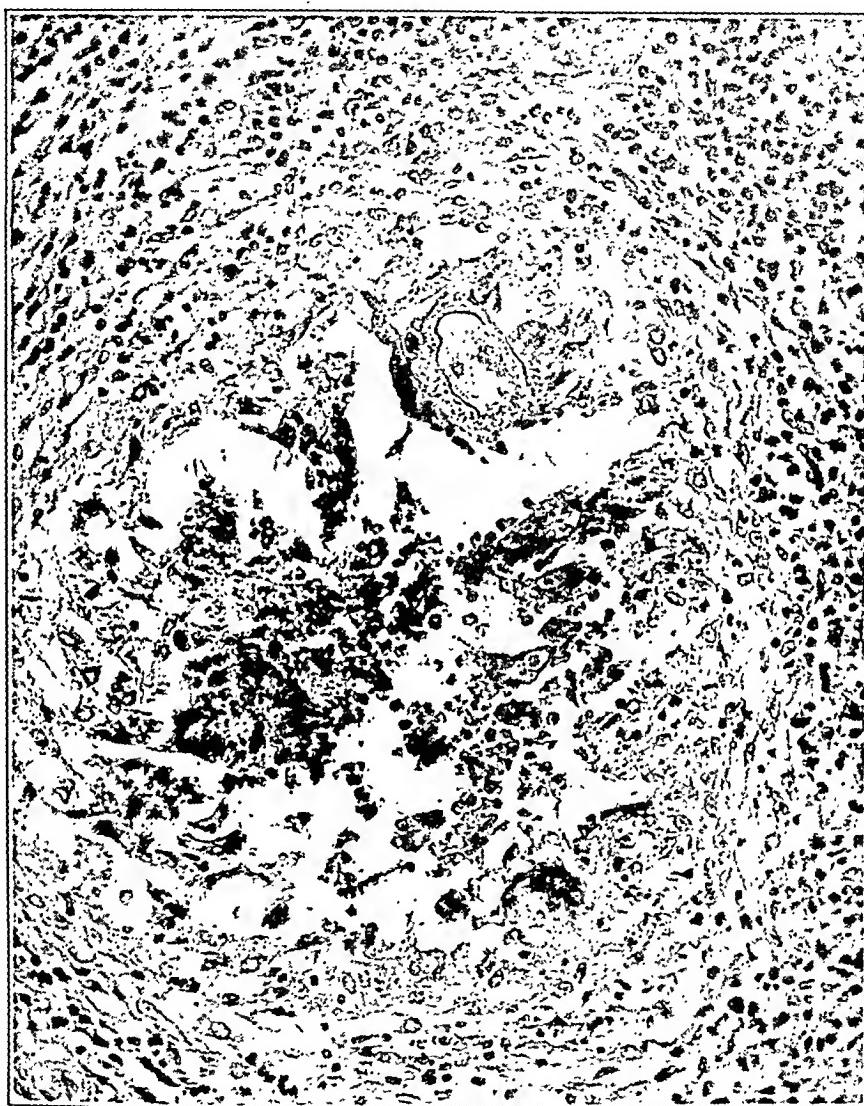
Fig. 3 (case 1).—Photomicrograph of submucosal pseudotubercles. × 400.

Twenty per cent of the white blood cells were eosinophilis, and the white cell count was 10,200. The nonprotein nitrogen was 32 mg. per hundred cubic centimeters, globulin 2.5 Gm. per hundred cubic centimeters, and the formaldehyde gel reaction negative. The icterus index was 4, serum bilirubin 0.1 mg. per cubic centimeter and the reading for the cephalin flocculation test with the Difco antigen was 2 plus. The bromsulfalein test showed 6 per cent retention of the dye stuff at forty-five minutes. From the combined clinical and laboratory data it appeared at the time of death that there were no symptoms or laboratory findings suggestive of active disease due to Schistosoma japonicum except

that there was still an eosinophilia and slight retention of bromsulfalein. Death occurred by strangulation about seven months after the onset of the disease.

Autopsy.—At autopsy it was obvious, as is seen in the photomicrographs (figs. 4 and 5), that there still was active hepatic disease. The liver weighed 1,674 Gm. and contained scattered small white nodules which were up to 3 mm. in diameter on the surface and up to 6 mm. in diameter in the liver substance. The surface of the liver was otherwise smooth. Similar nodules pre-

Fig. 4 (case 2).—Photomicrograph of liver showing circumscribed abscess. × 100.

sented themselves in the heart, in which there was gross evidence of mitral stenosis. The intestines apparently were normal, but no sections were taken by the prosector.

Microscopic examination of the liver showed that there were small circumscribed definite abscesses (fig. 4) with focal necrosis of parenchyma and also pseudotubercle formations (fig. 5) with partial fibrotic replacement characteristic of a healing phase. There was no fatty degeneration or evidence of a developing cirrhosis. Microscopic examination of nodules which grossly appeared like those in the liver was made from many areas of the myocardium. These

failed to disclose the presence of any abscess formation but there were focal areas with accumulations of large mononuclear cells, occasionally forming giant cells. No eggs were demonstrated in these collections. It was necessary to consider these formations as possible Aschoff bodies in view of the history of chorea and the mitral stenosis. Considering the length of time elapsed from the original episode, the cellular reaction was too extensive for Aschoff bodies.
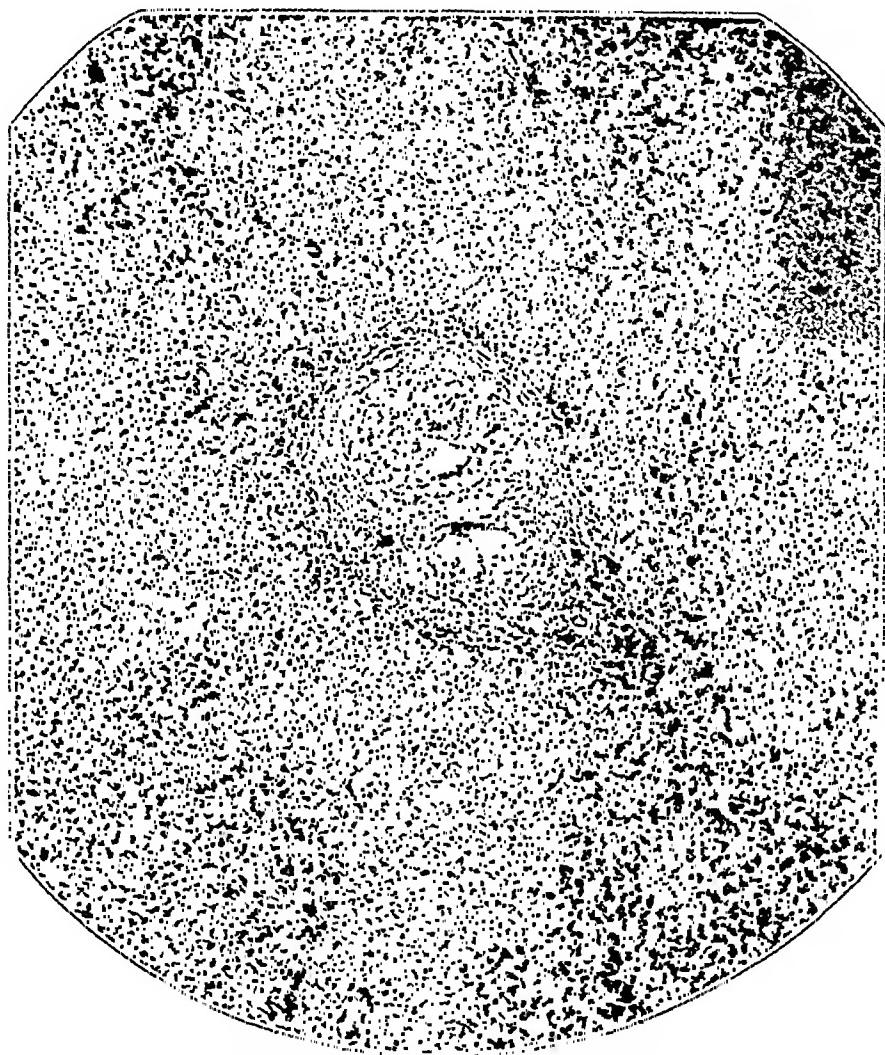
Fig. 5 (case 2).—Photomicrograph of liver showing pseudotubercle formations. × 50.

METHODS

Bromsulfalein.[3]—The amount of dye injected intravenously was 5 mg. per kilogram of body weight. The permanent standards used were supplied by Hynson, Westcott and Dunning. Since the standards were prepared for the 2 mg. test, the calculations were made by dividing the readings obtained by 2.5.

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3. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods: Rosenthal's Bromsulfalein Method, ed. 10, Philadelphia, W. B. Saunders Company, 1943, p. 428.

Retention up to 4 per cent at forty-five minutes was considered normal.[4] However, in order to exclude all possible borderline values, in this study 8 per cent retention of the dye was considered to be the lowest abnormal value.

Galactose Tolerance Test.—Forty grams of galactose were given by mouth to fasting subjects. The amount of sugar excreted in the urine during the next five hours was determined by Benedict's quantitative method using a solution which had been standardized against galactose. The results were reported as galactose, and an excretion of over 3 Gm. in the five hour period was considered abnormal.

Intravenous Test for Hippuric Acid.[5]—Sodium benzoate (1.77 Gm.) was injected intravenously, and the urinary excretion of hippuric acid for a period of one hour was determined. Excretion of less than 0.80 Gm. was considered abnormal.[4] The hippuric acid was salted out of the acidified urine with ammonium sulfate (0.5 Gm. per cubic centimeter) at 20 C. for one hour. The precipitate was filtered with suction and was washed with three 5 cc. portions of ice cold water. In the calculation of the results, correction for the solubility of hippuric acid was made by adding 0.1 Gm. per hundred cubic centimeters of urine to the weight of precipitate obtained.

Icterus Index.—The color of the serum was compared with those of standard potassium dichromate solutions in 75 by 12 mm. test tubes. The serum was then diluted 1:2 and 1:3 with isotonic solution of sodium chloride, and the colors of these dilutions were matched with the standards as checks on the original value obtained. With an occasional serum, poor checks were obtained with the two dilutions, and in such a case the serum was diluted further until consistent values were obtained. A value of over 8 units was considered abnormal.[4]

Serum Bilirubin.[6]—The method used was the Thannhauser-Anderson modification of the van den Bergh test. The permanent cobalt sulfate standards of McNee and Keefer were used. A value of over 0.50 mg. per hundred cubic centimeters was considered to be abnormal[4]; however, in order to exclude all possible borderline values, in this study a value of 0.80 mg. per hundred cubic centimeters was considered to be the lowest abnormal value.

Urine Urobilinogen.[7]—A modification of the Wallace and Diamond serial dilution method was used on fresh morning specimens. Tests were routinely performed on a 1:5 dilution. Urine specimens yielding positive reactions in this dilution were diluted further and tested again. The highest dilution in which a positive reaction was obtained was recorded. A positive reaction in a dilution of more than 1:20 was considered abnormal.

4. Lippincott, S. W.; Hesselbrock, W. B.; Ellerbrook, L. D.; Gordon, H. H., and Rhees, M. C.: Normal Values for Certain Tests of Liver Function in Healthy Soldiers, Am. J. Clin. Path., **16**:188, 1946.

5. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, ed. 1, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 325.

6. Thannhauser, S. J., and Anderson, E.: Methodik der quantitativen Bilirubin-Bestimmung in menschlichen Serum: Ueber die Ehrlich-Proschersche Reaction, Deutsches Arch. f. klin. Med. **137**:179, 1921. McNee, J. W., and Keefer, C. S.: The Clinical Value of the van den Bergh Reaction for Bilirubin in Blood, With Notes on Improvements in Its Technique, Brit. M. J. **2**:52, 1925.

7. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

RESULTS OF TESTS OF HEPATIC FUNCTION

Initial Evaluation.—Results of tests of patients' hepatic function after arrival in this hospital are shown in table 1. All values for serum albumin were normal. The serum globulin values were elevated in 8 patients but only to a minimal extent and were considered inconsequential. As would be expected from this the formaldehyde gel test elicited a negative reaction in all but 1 case. At this time all but 4 per cent of the icterus index values and 6 per cent of the serum bilirubin values were normal. All tests for urobilinogen in the urine gave normal results. In the intravenous hippuric acid test, 5 per cent of the persons tested had a value below 0.80 Gm., but it has been shown [4] that even in normal persons occasional values below this level occur, usually because of incomplete emptying of the bladder. Four per cent of those given the galactose tolerance test gave abnormal reactions, but again the amount excreted above the normal was minimal.

TABLE 1.—*Results of Initial Tests of Liver Function on Return from Overseas*

Type of Test	Number of Men	Normal Tests		Abnormal Tests	
		Number	Per Cent	Number	Per Cent
Globulin	175	167	95	8	5
Formol gel	84	83	99	1	1
Icterus index	162	155	96	7	4
Serum bilirubin	246	231	94	15	6
Urobilinogen	85	85	100	0	0
IV hippuric	108	103	95	5	5
Galactose	189	182	96	7	4
Bromsulfalein	245	215	88	30	12

The most significant alteration of results in the hepatic function tests is seen in the bromsulfalein figures, in which 12 per cent of the patients had abnormal values. This test and that for serum bilirubin are discussed later in detail because of their relationship to treatment. In the 12 per cent of patients with initially abnormal bromsulfalein values and in the 6 per cent of patients with initially abnormal bilirubin levels, no correlation was found with jaundice, proved or suspected, during the acute phase of the illness overseas; with the presence of the eggs of Schistosoma japonicum in the stools examined at this hospital, or with symptoms on their arrival here. An elevated serum bilirubin during the initial evaluation, however, was associated three times as frequently with an abnormal bromsulfalein retention as was a normal serum bilirubin. Of 16 patients whose stools were repeatedly negative on examination in this hospital and who had varying degrees of abnormal bromsulfalein retention on initial evaluation, 10 on reexamination more than one month later gave normal reactions to the tests.

Bromsulfalein Test During Treatment.—The bromsulfalein test was performed on patients during and after treatment with two trivalent

antimony compounds (fuadin, and antimony and potassium tartrate), on patients whose stools were found to contain the eggs of Schistosoma japonicum (table 2, figure 6). The various courses of treatment lasted from twenty-five to forty-one days with injections of fuadin (intramuscularly) or of antimony and potassium tartrate (intravenously) being given every other day. The strength of the solutions used and

TABLE 2.—*Percent Incidence of Abnormal Reactions to Bromsulfalein Tests in Relation to Treatment at Harmon General Hospital*

		Number of Determinations					
					Days After End of Treatment		
	Result of Bromsulfalein Test	Before Treatment	During Treatment	End of Treatment	30-59	60-89	90 or More
Antimony and potassium tartrate 0.5% solution 320 cc.	0-4%...............	60 (90%)	56 (84%)	42 (65%)	31 (70%)	28 (67%)	9 (90%)
	6%................	5 (7%)	5 (7%)	13 (20%)	5 (11%)	3 (6%)	0
	8% or more........	2 (3%)	6 (9%)	10 (15%)	8 (19%)	11 (26%)	1 (10%)
	Number of patients	52	51	63	42	42	10
Antimony and potassium tartrate 0.5% solution 416 cc.	0-4%...............	22 (79%)	20 (66%)	10 (59%)	1 (33%)		
	6%................	6 (21%)	4 (14%)	2 (12%)	2 (67%)		
	8% or more.........	0	6 (20%)	5 (29%)			
	Number of patients	24	20	13	3		
Fuadin 1st course 6.3% solution 65 cc.	0-4%...............	21 (64%)	14 (74%)	19 (44%)	13 (54%)	4 (40%)	1
	6%................	6 (18%)	2 (10%)	9 (21%)	6 (25%)	2 (20%)	
	8% or more........	6 (18%)	3 (16%)	15 (35%)	5 (21%)	4 (40%)	
	Number of patients	33	16	32	23	8	1
Fuadin 2d course 6.3% solution 65 cc.	0-4%...............	..	13 (62%)	7 (39%)	3 (37%)	5 (71%)	1
	6%................	..	3 (14%)	5 (28%)	1 (13%)	2 (29%)	
	8% or more........	..	5 (25%)	6 (33%)	4 (50%)		
	Number of patients	..	21	17	8	7	1
Fuadin 6.3% solution 105 cc.	0-4%...............	7 (47%)	8 (53%)	..	1		
	6%................	5 (33%)	2 (13%)				
	8% or more........	3 (20%)	5 (33%)				
	Number of patients	12	10	..	1		

the total amount given are recorded in the appropriate tables and figures. After the completion of a course of therapy, the patients were automatically released on a thirty day furlough, returning to the hospital for a follow-up period of two to three weeks followed by a second twenty day furlough before returning for their final evaluation. Tests of hepatic function were made at these times.

To patients whose stools were again found to contain the ova of Schistosoma japonicum during the follow-up period, treatment was

given a second time with the same course of therapy. Their bromsulfalein studies before the second course of treatment were among those in the follow-up period and were, therefore, on the whole higher than those before their initial treatment at this hospital. In figure 6 these are recorded in the appropriate follow-up period and are not included in the levels before treatment.

As can be seen in table 2 and figure 6, there was a distinct tendency for the incidence of abnormalities in the bromsulfalein test to increase significantly while treatment was being given, at the end of treatment and during the follow-up periods. The inclusion in the figures of borderline abnormalities added nothing to the general trend.
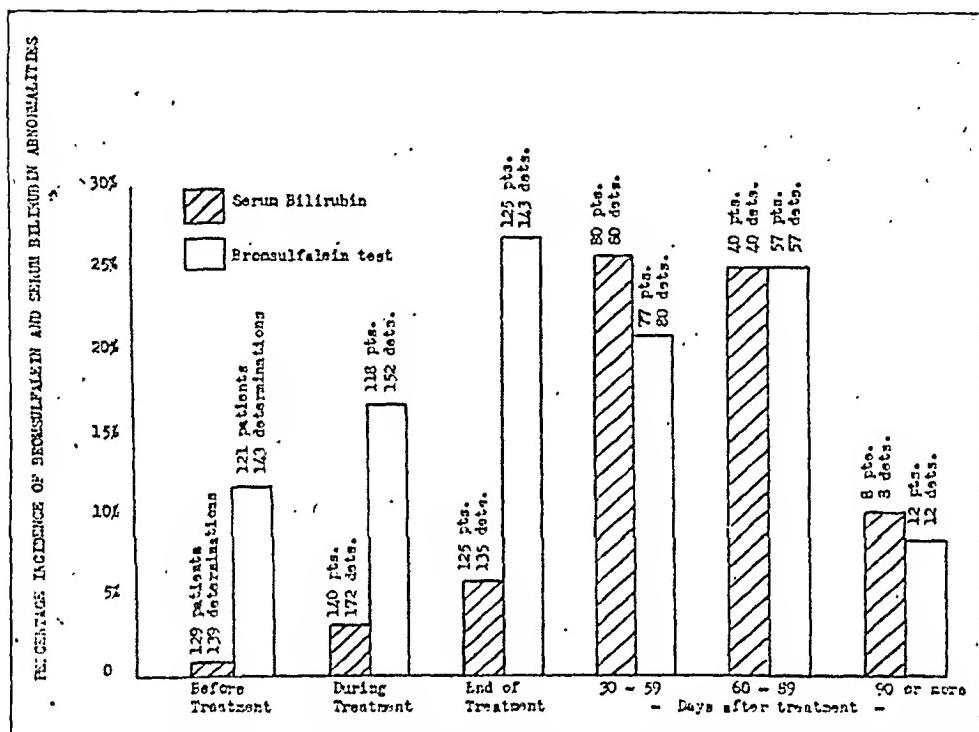
Fig. 6.—The relationship of the incidence of abnormalities in bromsulfalein tests and serum bilirubin concentrations to treatment at Harmon General Hospital. All types and courses of treatment.

In the few cases studied ninety or more days after the cessation of therapy, the incidence of bromsulfalein abnormalities had dropped to the level before treatment, but the number of cases is too small to justify any conclusions. In this regard, it is of interest that of 111 patients examined within three months after treatment overseas with fuadin, 10 (9 per cent) had abnormal reactions to bromsulfalein. Of 61 similarly examined more than three months after fuadin treatment overseas, 4 (7 per cent) had an abnormal reaction to bromsulfalein. All of 11 patients who had no treatment overseas gave initially normal reactions to bromsulfalein tests. The stools of 6 of these untreated patients were found to contain the ova of Schistosoma japonicum at this hospital.

In figures 7 and 8 are recorded individual cases followed through various courses of therapy. In each instance there were at least four determinations at different periods of study during the initial course. At each period only one determination per patient was recorded; if two had been done, the higher was recorded in each instance. In these individual cases repeatedly examined, the same general trend of the incidence of bromsulfalein abnormalities is noted as in the over-all picture, shown in figure 6. The same is true of the second course of the same therapy. The cases in which determinations were done during a third course of treatment at this hospital are too few to justify any conclusions.

TABLE 3.—*Percent Incidence of Abnormal Serum Bilirubin Concentrations in Relation to Treatment at Harmon General Hospital*

		Number of Determinations					
					Days After End of Treatment		
	Serum Bilirubin Results	Before Treatment	During Treatment	End of Treatment	30-59	60-89	90 or More
Antimony and potassium tartrate 0.5% solution 320 cc.	0-0.7 mg.%.........	66 (99%)	77 (96%)	64 (96%)	35 (74%)	18 (72%)	7
	0.8 mg.% or more...	1	3 (4%)	3 (4%)	12 (26%)	7 (28%)	
	Number of patients	62	64	66	47	25	7
Antimony and potassium tartrate 0.5% solution 416 cc.	0-0.7 mg.%.........	28 (100%)	26 (81%)	14 (93%)	2		
	0.8 mg.% or more...	0	6 (19%)	1 (7%)	1		
	Number of patients	24	22	14	3		
Fuadin 1st course 6.3% solution 65 cc.	0-0.7 mg.%.........	33 (100%)	27 (100%)	35 (97%)	15 (71%)	5 (63%)	
	0.8 mg.% or more...	0	0	1 (3%)	6 (29%)	3 (37%)	
	Number of patients	32	26	29	21	8	
Fuadin 2d course 6.3% solution 65 cc.	0-0.7 mg.%.........	..	15 (83%)	14 (82%)	6 (75%)	7	1
	0.8 mg.% or more...	..	3 (17%)	3 (18%)	2 (25%)		
	Number of patients	..	18	16	8	7	1
Fuadin 6.3% solution 105 cc.	0-0.7 mg.%.........	10 (99%)	12 (80%)	..	1 (100%)		
	0.8 mg.% or more...	1 (1%)	3 (20%)		1		
	Number of patients	11	10	..	1		

It is clear from these studies that no obvious difference was demonstrated by the bromsulfalein test between the various types and courses of treatment.

Serum Bilirubin During Treatment.—A quantitative serum bilirubin determination was made in almost every instance when the bromsulfalein test was done. The results of all such determinations are recorded in figure 6 and table 3 in the same manner as the results of the bromsulfalein tests.

Here again there was a distinct tendency for the incidence of abnormal serum bilirubin concentrations to rise in relation to treatment, but this

rise came later than that of the bromsulfalein, the major incidence occurring in the first follow-up period, on return from the thirty-day post-treatment furlough. Also again there· is a tendency in the few cases followed for more than ninety days for the abnormalities to return to the level before treatment, with, however, too few cases to justify any conclusions. Determinations during the second course of treatment were recorded in the same way as for the bromsulfalein studies. The inclusion in the figures of borderline abnormalities added nothing to the general trend. It is interesting that, as compared with the pretreatment studies, no correlation was found to exist between the abnormal results of bromsulfalein tests and the abnormal serum bilirubin levels when contemporaneous determinations of these two were compared during treatment or during the follow-up period.

In figures 7 and 8 are also recorded individual cases followed through various courses of therapy with multiple determinations of the serum bilirubin concentration. The same method of recording these levels was used as in the results of the bromsulfalein test. It appears from these individual cases that the same general trend of the incidence of serum bilirubin abnormalities was present as in the over-all figure 6 with a definite trend for values of the serum bilirubin to increase with a passage of time in relation to therapy. Also it is apparent from these studies that no obvious difference was demonstrated by the serum bilirubin between the various types and courses of treatment. There was no indication that this was due to hemolysis because there was no apparent change in the erythrocyte count during or after treatment.

It is important to note in the studies of the results of the bromsulfalein and bilirubin tests that the degrees of abnormality were not great. Thus the majority of the bromsulfalein abnormalities were between 8 per cent and 12 per cent dye retention and the majority of the bilirubin abnormalities were between 0.8 and 1.2 mg. per hundred cubic centimeters. None was of the degree commonly associated with clinically severe hepatic disease.

COMMENT

In evaluating hepatic function in this group of persons it is important to consider the limited extent of the disease as shown by the findings in the 2 autopsies and the limited toxic effects associated with antimony treatment as noted in the results of the tests of hepatic function. The autopsy findings as illustrated in the photographs indicate clearly in our 2 cases of disease of seven months' duration, in which insufficient treatment[8] was given, that the hepatic lesions associated with seeding of eggs were circumscribed, tended to become fibrotic and left almost all of the liver intact. There was no indication of coalescence of lesions from

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8. Schistosomiasis Japonica, United States War Department Technical Bulletin (TB Med 167), Washington, D. C., Government Printing Office, June 1945.
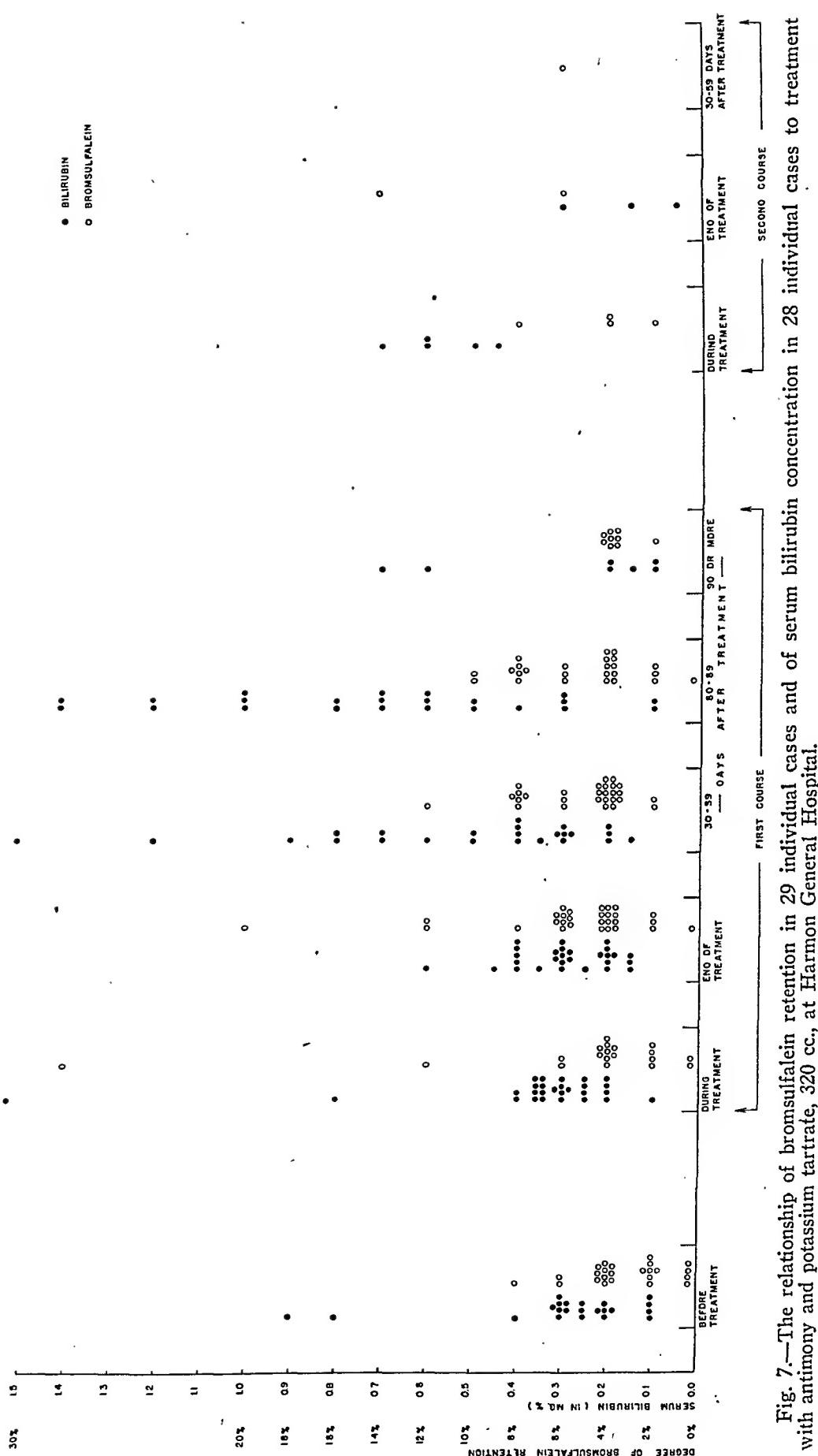
Fig. 7.—The relationship of bromsulfalein retention in 29 individual cases and of serum bilirubin concentration in 28 individual cases to treatment with antimony and potassium tartrate, 320 cc., at Harmon General Hospital.

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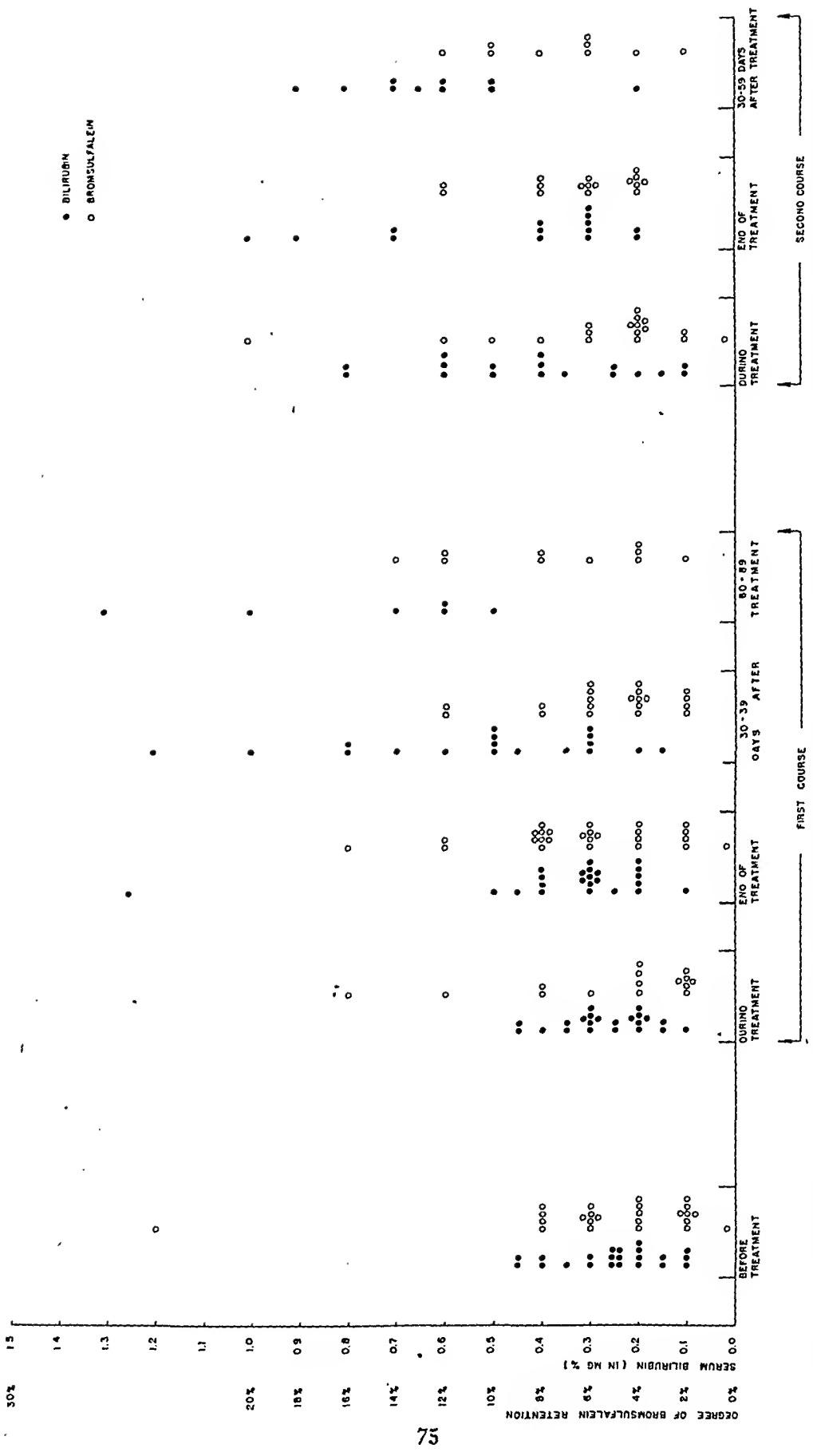
Fig. 8.—The relationship of bromsulfalein retention in 26 individual cases and of serum bilirubin concentration in 23 individual cases to treatment with fuadin, 65 cc., at Harmon General Hospital.

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the portal spaces or extension of fibroblastic connective tissue to interrupt or isolate functioning lobules. In support of these pathologic findings are the initial studies of hepatic function which show a low incidence of dysfunction.

Whether the stated abnormalities in the results of the bromsulfalein tests and the serum bilirubin concentrations found in association with treatment are due to primary toxic effects of antimony [9] or are due to secondary effects is not known. It remains to be decided whether repeated courses of antimony can be given with impunity.

SUMMARY AND CONCLUSIONS

The pathologic lesions observed at autopsy in 2 patients in a group of 481 American soldiers with schistosomiasis japonica are presented together with the results of serial tests of hepatic function done before, during and after antimony treatment in a large number of these patients.

The lesions observed were in the large and the small intestine and the liver. They consisted of either minute frank abscesses or fibrotic nodules. One of the cases showed myocardial lesions possibly due to this disease. There was no indication morphologically in these 2 cases at this stage of the disease that damage to the liver sufficient to impair its function had occurred.

The initial studies of hepatic function in these patients on return to this country from overseas showed the following incidence of abnormal results: globulin, 5 per cent; formaldehyde gel 1 per cent; icterus index, 4 per cent; serum bilirubin, 6 per cent; urobilinogen, 0 per cent; intravenous test for hippuric acid, 5 per cent; galactose tolerance, 4 per cent, and bromsulfalein retention, 12 per cent.

Repeated bromsulfalein tests and serum bilirubin determinations showed a definitely increased incidence of mild abnormalities toward the end of and after treatment with trivalent antimony compounds. This increased incidence persisted for at least ninety days after the cessation of treatment. In a small group of cases followed beyond ninety days, the incidence was markedly decreased. The evidence suggests that antimony treatment has a minor direct or indirect effect on the liver.

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9. Khalil, M.: The Specific Treatment of Human Schistosomiasis, Arch. f. Schiffs- u. Tropen-Hyg. **35**:1, 1931; cited by Schmidt, H., and Peters, F. M.: Advances in the Therapeutics of Antimony, Leipzig, Georg Thieme, 1938. Weese: Ueber experimentelle Nierenschaedigungen durch Fuadin und Brechweinstein, Abhandl. d. Med. u. Chem. **3**:412, 1936. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 1, New York, The Macmillan Company, 1941, p. 748.

IMMERSION HYPOTHERMIA

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THE EFFECTS of freezing have been described in experimental hypothermia. The purpose of this article is to describe a clinical syndrome, herein to be called "immersion hypothermia," which is the result of immersion in the sea in latitudes where the temperature of the water is below approximately 65 F.

During the year 1944 approximately 150 men who had been immersed in the waters of the North Sea were seen by medical officers [1] at the United States Army Air Forces fighter station at Martlesham Heath, Suffolk County, England, all of whom contributed to the study of this problem. In all instances these patients were flying personnel of the United States Army Air Forces or Royal Air Force who had been on operational missions over enemy-occupied territory of the European continent. For a variety of reasons they were forced to abandon their aircraft by ditching [1a] or by bailing out into the North Sea. Most were picked up by rescue launches of the Royal Navy or the Royal Air Force and brought to the dock at Felixstowe, England, 8 miles (12.8 kilometers) distant from Martlesham, to which they were taken by ambulance. A few were rescued by Walrus amphibians of the Air-Sea Rescue Squadron of the Royal Air Force and flown directly to the airfield. Except for these few, most patients were not seen by a medical officer for several hours after the immersion.

The majority of the men showed no immediate effects other than temporary fatigue. In a statistical study to determine the factors involved in the survival of flying personnel whose aircraft became unserviceable over the English Channel and the North Sea, Mazer and Sheeley [2] collected the data on a large number of persons, including some of the data in the cases to be described here. Among 192 men picked up from

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1. These medical officers included Major Robert E. Nuernberger and Captains Walter Baumgarten, Roland Faulkner, Edward L. Higgins and Anthony Zachmyc as well as Squadron Leader Rouillard, of the Royal Air Force Station, Felixstowe, England.

1a. Ditching denotes the forced descent of an airplane on the water. The expression probably had origin in the reference to the North Sea as "The Big Ditch."

2. Mazer, M., and Sheeley, W. R.: Project no. 198, First Central Medical Establishment, U. S. Army Air Forces, Feb. 3, 1945.

various kinds of aircraft, 163 survived. Of the 29 who died, all but 3 were dead at the time of rescue.

The patients in the following reports of cases were all seen personally. Included are patients who demonstrated little pathologic change to contrast with those who showed a considerable amount despite a similar length and degree of exposure (table 1).

REPORT OF CASES

CASE 1.—The Liberator in which the patient, aged 20 years, was a crewman crashed into the North Sea, latitude 54° 04' north and longitude 01°, 54', 02" east, at 12:53 p. m. on July 20, 1944. At 1:10 p. m. a launch reached the position. One other member of the crew (the patient in case 2 in this series) of the Liberator was rescued by this boat. Both men had been immersed in water with a temperature of 58 F. for approximately twenty minutes.

The patient was failing rapidly and swallowing a considerable amount of water when he was picked up. He was not unconscious but was extremely weak and was coughing. The pulse rate was reported as strong and regular. His memory was hazy for about six hours after the time of the crash. As soon as he was brought aboard he was placed in the prone position, then elevated by the hips to drain all the water which came from the mouth and then given artificial respiration (Schaefer method) for five minutes ("because of weakness and coughing"). His clothes were replaced by woollens, and he was covered by blankets. After a half-hour, during which he continued to moan and groan in apparent semi-consciousness, he quietly went to sleep. He woke four hours later, feeling much better. Before going to sleep he urinated and had a copious stool with passage of water (salt water?) from the bowel.

Six hours and twenty minutes after rescue he arrived at the Felixstowe pier and was taken immediately to Royal Air Force sick quarters. He was rational, well oriented, generally weak and somewhat pale and grayish. The skin felt normal. The oral temperature was 100.2 F. The pulse rate was obtained with difficulty, was slow and apparently regular and varied from 76 to 81. The arterial blood pressure ranged from 96 to 106 systolic and 54 diastolic. The heart rate was at first regular. The sounds were extremely faint. No murmur was heard. The systolic pressure came through the blood pressure cuff with irregular strength; for a time this irregularity was fairly constant as a failure of every fourth beat to manifest itself. Later the total arrhythmia became evident by cardiac ausculta-tion. Over the medial portion of the lower lobe of the left lung there was hyper-resonance and an absence of breath sounds. Lateral to this area was a region in which diminished vesicular breath sounds were heard. The diagnosis of auricular fibrillation and atelectasis of the lower lobe of the left lung was made clinically.

The patient was transferred by ambulance to the sick quarters at Martlesham Heath. At 8:40 p. m. (seven and a half hours after rescue) the temperature was 100 F., the pulse rate 76, the respiratory rate 24 and the systolic blood pressure 100. The diastolic pressure was unobtainable. One hour later the rate was around 100, and a loud diastolic murmur was heard over the precordium. After another half-hour (fifteen to twenty minutes after a cup of hot coffee was given) the pulse rate was strong and regular at 60 beats per minute. The heart sounds were strong, and the diastolic murmur was extremely soft and blowing in character. Because of the continually changing character of the cardiac obser-vations and the continued irregularity with which sounds came through the sphygmomanometer cuff, it was thought that fibrillation might still be present.

TABLE 1.—*Summary of Important Clinical and Laboratory Data in Six Persons Rescued from Immersion in the North Sea*

Case	Name and Date of Immersion	Age, Yr.	Ball or Ditch	Time In Sea	Water Temperature, F.*	Time In Wet Clothes	Time After Rescue Before Observation, Hr.	Temperature on First Observation, F.	Pulse Rate	Blood Pressure	Psychic Changes	Blood Analysis	Electrocardiogram
1	S/Sgt. R. M. (July 20, 1944)	21	Ditch	20 min.	58	10 min.	3½	100.2 (rectally)	76 to 81	96 to 106/51	Semicoma	Normal	Auricular fibrillation and flutter
2	Sgt. O. A. (July 20, 1944)	23	Ditch	20 min.	58	10 min.	9	99.4 (rectally)	70	116/55	None	Normal	Not done
3	1/Lt. E. C. W. (Sept. 9, 1944)	23	Ball	40 min.	61	2 hr.	6	99 (orally)	84	130/34	Transient hysteria; semicoma, 1 hr.	Normal	Minimal prolongation of P-R interval
4	1/Lt. R. G. G. (Sept. 13, 1944)	25	Ball	60 min.	60	2 hr.	7	99 (orally)	60	96/58	None	Not done	Minimal prolongation of P-R interval
5	1/Lt. V. W. (Oct. 8, 1944)	22	Ball	40 min.	61	12 hr.	3	98.6 (orally)	82	128/83	None	Not done	Normal
6	1/Lt. H. H. L. (Dec. 29, 1944)	21	Ditch	35 min.	43	30 min.	½	93 (rectally)	63 to 102	95 to 120/70 to 85	Coma	Hemoconcentration; hyperglycemia	Auricular fibrillation and flutter

* Obtained from Meteorological Branch, Royal Navy.

TABLE 2.—*Analysis of Blood Taken from Patients after Immersion in North Sea*

Case	Time After Rescue Hr.	Hemoglobin Content, Gm./100 Cc.	Red Blood Cell Count	White Blood Cell Count	Differential Count			Specific Gravity (Whole Blood)	Specific Gravity (Plasma)	Plasma Proteins, Gm./100 Cc.	Hematocrit Reading, Vol./100 Cc.	Nonprotein Nitrogen (Whole Blood), Mg./100 Cc.	Creatinine (Whole Blood), Mg./100 Cc.	Sugar (Whole Blood), Mg./100 Cc.	Chlorides (Whole Blood), Mg./100 Cc.	Potassium (Whole Blood), Mg./100 Cc.	Phosphorus (Whole Blood), Mg./100 Cc.	Calcium (Serum), Mg./100 Cc.
					Neutrophils, %	Lymphocytes, %	Monocytes, %											
1	11	17.0	5,490,000	13,800	76	15	9	1.062	1.027	6.8*	50.0	28.8	1.5	100	470	..	4	11.1
2	11	15.5	......	......	..	..	..	1.059	1.027	6.8*	....	23.6	1.4	98	470	..	3.6	11
3	10	15.8	......	......	..	..	..	1.059	1.026	6.5	47.0	40.0	...	...	610	28	...	...
6	½	16.4	5,060,000	15,900	25	75	0	1.063	1.031	8.2	48.5	....	...	308	482	..	...	...
6	72	16.0	4,700,000	4,000	36	64	0	1.060	1.027	6.5	47.0	28.0	...	66	445	26.7	...	...

* Protein partitions normal.

The chest was resonant and the breathing vesicular. His improved condition allowed for transfer to the Two Hundred and Thirty-First Station Hospital. On arrival there, twelve hours after rescue, he was calm, well oriented and without complaint. The heart rate was slow, 60 per minute, and there was slight irregularity. On the next morning, physical examination showed normality except for a few moist rales heard over both lungs posteriorly. The heart rate was regular at 70 beats per minute.

A roentgenogram of the chest made on July 21 showed small pneumonic areas in the lower lobes of both lungs. In the hospital the temperature never exceeded 99.5 F., and it was normal on the third day. The lungs cleared rapidly; a second roentgenogram of the chest, on July 25, showed clearance of the areas of pneumonitis noted on the patient's admission.

Although the surgeon at the hospital considered the heart normal, an electrocardiogram was taken twelve hours after rescue, because of the previous diagnosis of auricular fibrillation. It revealed auricular fibrillation alternating with impure flutter; the ventricular rate was 60 and almost regular in rhythm. A second electrocardiogram, twenty hours after rescue, showed normal sinus rhythm with a P-R interval of 0.20 seconds and normal QRS complex. A third electrocardiogram, six days later, was similar to the second one.

Blood drawn eleven hours after rescue was analyzed at the Sixty-Fifth General Hospital and yielded normal results (table 2). The urine showed no abnormalities.

The therapy was symptomatic, and recovery was uneventful. A month later the patient was reported by the surgeon of his squadron to be in good condition physically and mentally.

Summary.—The period of immersion was twenty minutes; the patient was failing rapidly and swallowing water when rescued. There were weakness and partial loss of consciousness during the first six hours. When first seen at the end of this time the patient showed clinical evidence of shock, auricular fibrillation and atelectasis of the lower lobe of the left lung. Auricular fibrillation and impure flutter were demonstrated by electrocardiogram twelve hours after his removal from the water. Normal sinus rhythm was present both twenty hours after and six days later. A roentgenogram showed small pneumonic areas in the lower lobe. Immediate therapy included artificial respiration, drying and application of warm coverings.

CASE 2.—The patient, aged 21 years (from the same aircraft as the patient in case 1), was immersed for the same length of time. He sustained several lacerations from the crash but was otherwise in good condition physically and mentally. He was cheerful, quiet and well oriented when first seen, six and a half hours after rescue. The heart was strong, loud and regular. No murmur was heard. The lungs were clear and resonant. The temperature was 99.4 F. by mouth, the pulse rate 70, the blood pressure 116 to 122 systolic and 50 to 30 diastolic. One hour later the temperature was 99 F., the pulse rate 100, the respiratory rate 20 and the blood pressure 116 systolic and 74 diastolic.

He was sent to the Sixty-Fifth General Hospital for admission. Blood taken for analysis approximately eleven hours after rescue yielded normal results (table 2).

A follow-up report from the surgeon of his squadron a month subsequent to immersion stated that the patient was in good physical and mental condition.

Summary.—The conditions of immersion were similar to those in case 1, except for addition of a wound sustained from the crash. No physiologic reaction was observed except for postimmersion elevation of temperature.

CASE 3.—The patient, aged 23 years, bailed out of his P-51 fighter plane at a height of 4,000 feet (1.2 kilometers) about 7 p. m. on Sept. 9, 1944. After being immersed in the North Sea for a few minutes, he got into his dinghy without difficulty. The Walrus aircraft reached him about 7:40 p. m. In trying to reach him the Walrus punctured the dinghy. He suffered a slight contusion of the scalp from striking the Walrus and was again immersed in the sea for a period of thirty minutes. The temperature of the water was approximately 58 F. He was reported to be hysterical and would not grasp a rope thrown to him. When finally pulled aboard he was shivering violently; the exposed parts of the body were cyanotic. Foam issued from the mouth during a short period of artificial respiration. He was wrapped in blankets and in a few minutes went to sleep (or lapsed into coma?). Thirty minutes later he woke, still complaining of the cold. The Walrus had been damaged and sank slowly, going under water just as the rescue motor launch hove to. The patient was unable to help himself. The master of the launch dove in and brought him to the boat. On board the launch he appeared to be in deep shock. He was pale and could not answer questions although he seemed to understand. He suffered from subjective cold sensations and shivering for an hour continuously and then for another several hours intermittently. He was dried, placed in warm clothing and given artificial respiration and 1 ounce (29.6 cc.) of brandy. He slept for several hours. When first seen by a medical officer, at 3 a. m. on September 10, his condition seemed good.

He was first under observation at station sick quarters on September 10, thirteen hours after rescue. His temperature was slightly elevated. The pulse rate, respiratory rate and arterial blood pressure were within normal limits. His mental status was normal except that he had no memory of events from the time of his being picked up by the Walrus to the later rescue by the launch. An electrocardiographic tracing taken over fifteen hours after he had been removed from the sea showed a P-R interval of 0.20 seconds as compared with a P-R interval of 0.18 seconds in a control tracing made two days later. Auscultation of the heart at the time of the first electrocardiogram revealed only somewhat distant sounds. Analysis of blood taken at the time the electrocardiogram was made gave essentially normal results.

Summary.—There was repeated immersion and rescue. Apparent severe shock, disorientation, amnesia and coma were evidenced. Fifteen hours later the patient had slight elevation of temperature, and possible prolongation of the P-R interval was seen in an electrocardiogram. Other findings were normal.

CASE 4.—The patient, aged 25 years, was first seen at 7:30 p. m. on Sept. 13, 1944, seven hours after being rescued by a Walrus aircraft. He had been sixty minutes in water, the temperature of which was 60 F. The airplane was unable to ascend from the surface of the sea, and subsequently the patient was transferred to a motor launch. The rescuing pilot noted that the patient's eyes were open but unseeing. The patient had loss of memory for a period lasting two hours. When the patient was seen, his temperature was 99.2 F. by mouth, his pulse rate 100, with regular rhythm and his blood pressure 108 systolic and 76 diastolic.

He was admitted to sick quarters a half hour later, in apparently good condition. He was somewhat excited and restless. No other psychic disturbance was observed. The temperature was 99 F. by mouth, the pulse rate 60 and the blood pressure 96 systolic and 56 diastolic. The first cardiac sound appeared muffled. The pulse was labile. At 9 p. m. the electrocardiographic tracing showed a rate of 94, regular sinus rhythm and a P-R interval of 0.22 seconds, with slurring of the QRS complex, which was, however, not prolonged. The

temperature level returned to normal next morning. A control electrocardiographic tracing made a month later showed a P-R interval of 0.20.

Summary.—Immersion was for sixty minutes. Neuropsychiatric signs were present during the first two hours after rescue, disappearing completely within a short time. There was slight transient prolongation of the P-R interval.

Case 5.—The patient, aged 22 years, bailed out of his P-51 fighter aircraft shortly before dusk on Aug. 7, 1944 at longitude 51° 34′ 48″ north and latitude 02° 20′ 30″ east. He had to inflate his dinghy by hand and remained in the sea forty minutes (water temperature, 61 F.) before he was able to clamber into it. He floated in the dinghy for eighteen hours before rescue by a high speed launch of the Royal Air Force at 2:35 p. m. on August 8. After three hours on the launch he reached port and was seen by a medical officer. He had shivered throughout the night, but he felt better as soon as light dawned and he was able to dry his clothes and himself. On the launch he was given dry clothes, warm blankets and hot tea. When first seen, at 5:35 p. m. on August 8, he appeared in generally good mental and physical condition and had good color. The temperature was 98.6 F. orally, the pulse rate 82 and the arterial blood pressure 128 systolic and 88 diastolic. Auscultation of the heart revealed loud, distinct sounds and no murmurs. An electrocardiographic tracing at 8:20 p. m. was normal. No sequelae were observed.

Summary.—The patient spent forty minutes in the sea and eighteen hours in a dinghy during August. No ill effects were noted.

Case 6.—The patient, aged 21 years, was returning from a combat mission when trouble developed in the cooling system of the P-51 fighter aircraft in which he was flying. He attempted to bail out but found that the airplane lost altitude steadily. At 12:45 p. m. he ditched the aircraft in the North Sea 4 miles (6.4 kilometers) due east of Orfordness, Suffolk County (52° 6′ north and 0° 40′ east). In the crash he struck the gun sight and sustained a laceration of the upper lip as well as a contusion of the parietal region of the scalp. He swam free of the airplane and remained in the water for over thirty minutes. His life vest functioned well, but he was unable to get into his dinghy. The water seemed extremely cold (43 F.). He grew weaker and felt that he could last only a few minutes longer. At 1:15 p. m. a Walrus aircraft reached him and after a few minutes pulled him aboard. His clothes were not removed, and he remained cold and wet.

The Walrus landed at Martlesham Heath airdrome at 1:45 p. m. The patient was taken immediately to sick quarters. His clothes were removed, and he was covered by warm blankets and given light massage. At this time he was unconscious. The fingers and toes were cyanotic. The skin was extremely cold and tightly drawn. There were intense shivering, rigidity and involuntary shaking movements, which intermittently attained the proportion of clonic contractions of the limbs. There was also extreme restlessness, which necessitated three to four attendants for restraint. The eyes stared blindly to the front. The pupils were widely dilated and did not react to light. The veins were partially collapsed. The rhythm of the heart was totally irregular, and the rate averaged 68. The sounds came through with varying intensity and in general were distant. The temperature, blood pressure and pulse rate could not be obtained at first. Auricular fibrillation was diagnosed clinically. The patient appeared moribund.

Treatment was begun at once. Warm blankets were placed around the patient and light massage given. Blood plasma was administered intravenously. A total of 4 units in 1,600 cc. of fluid was given from 2 to 3:30 p. m. Warming was

attempted by means of blankets, hot water bags and light massage. After about twenty minutes it appeared that these methods were not proving effective. A heat cradle was then placed over the patient to warm him more rapidly and the blankets removed. The patient became quiet enough for estimation of temperature at 2:30 p. m., seventy-five minutes after rescue from the sea, at which time it was 93 F. by rectum and axilla. An hour later it was 95 F. rectally. The temperature reached 100.8 F. by mouth in six hours and remained elevated until thirty hours after rescue.

The heart rate ranged initially from 68 to 102 and then remained between 60 and 75 for the first hour; the rhythm and intensity of contraction were totally irregular. The arterial blood pressure range was 95 to 120 systolic and 70 to 85 diastolic. During the next three to four hours the heart rate became more rapid, while the sound of the contractions gradually grew louder; a soft systolic murmur
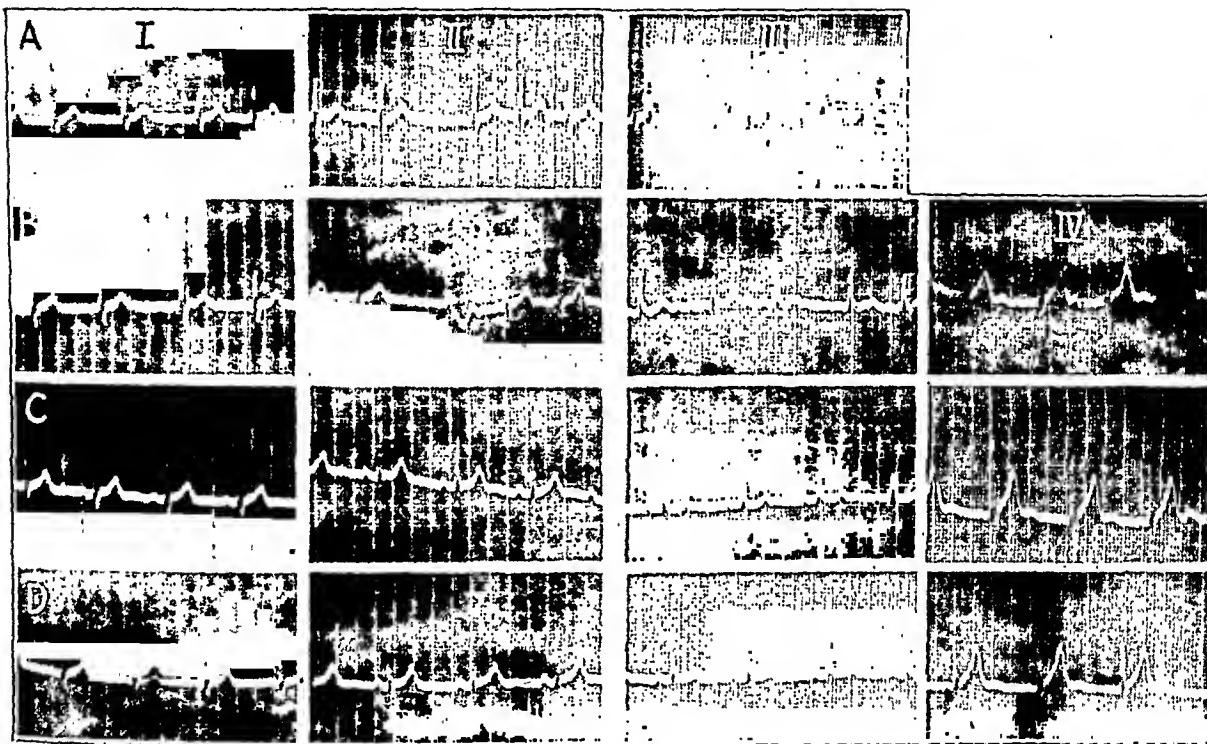
Electrocardiograms of patient (case 6) taken at intervals after rescue from immersion in the North Sea. *A,* one hour after rescue. Auricular fibrillation is present. A short sequence of flutter waves is seen in lead III. *B,* five hours after rescue. Auricular fibrillation persists. In lead II there is a ventricular extrasystole. In lead III flutter is again evident. *C,* ten and one-half hours after rescue. Normal tracing with sinus rhythm. *D,* twenty-four hours after rescue. The electrocardiogram is normal.

was heard intermittently. Electrocardiograms (fig.) at one and five hours after rescue demonstrated auricular fibrillation with short periods of flutter, during which there was an auriculoventricular ratio varying from 3 to 5 to 1. The ventricular complexes remained normal in spite of the slow response of the ventricles to auricular stimulus. Ten and a half hours after rescue the electrocardiogram revealed sinus regularity with a rate of 80. The electrocardiographic picture remained normal during the following two days.

The patient recovered consciousness gradually between one and two hours after rescue. With the return of consciousness he became and remained rational.

Neurologic examination toward the end of this period revealed no localizing signs. There was no abnormal psychiatric behavior and no evidence of neurotic tendency during more than three days of observation. Blood was removed for analysis at the time of admission to sick quarters. The results are shown in table 1. The most extraordinary observation was the decided hyperglycemia, the blood sugar content being 308 mg. per hundred cubic centimeters. The leukocyte count was 15,900, with 25 per cent neutrophils, as compared with a control three days later of 4,000 with 36 per cent. The blood nonprotein nitrogen was 40 mg. per hundred cubic centimeters, compared with 28 mg. three days later. A specimen of urine taken two hours after rescue contained a small amount of albumin.

Summary.—The patient was in extremely cold water (43 F.) for over thirty minutes, followed by another thirty minutes chilled in wet clothes. Coma lasted two hours. Considerable shock, subnormal temperature, auricular fibrillation with failing heart rate, hemoconcentration, apparent inversion of neutrophil-lymphocyte ratio and tremendous elevation of the blood sugar content were noted. The temperature gradually rose to a hypernormal level, and it slowly returned to normal thirty hours later. The cardiac rhythm became normal between five and ten hours after treatment was begun. In addition to the generally accepted method of slow warming by means of warm blankets, hot water bags and massage, a heat cradle was used and 1,600 cc. of blood plasma was administered intravenously. Empirically, these two procedures seemed to be more effective than the others.

CLINICAL PICTURE

The pathologic changes encountered in the syndrome of immersion hypothermia are of a progressive type. Mild degrees occur in many patients who appear entirely well by the time they are seen by a physician, while patients with hypothermia of severe degree may die before they can be seen. It was fortuitous that the first patient described was observed at a time when changes were apparent. In slightly altered circumstances he would have been kept quiet overnight and sent to the hospital the following day. Here the diagnosis of atypical pneumonia would have been made (as it was), and the matter would have gone no further.

As it is, the laboratory investigations presented in this report were not made soon enough after rescue, except in case 6. From case 6 alone can one gain a consecutive idea of the pathologic physiologic changes present. However, personal observations on patients mildly affected by hypothermia and a study of the material gathered by the First Central Medical Establishment of the Eighth United States Army Air Force[2] fit well enough so that one may draw a general clinical pathologic picture. There are decided changes in the cardiovascular system. The heart rate is usually slow soon after rescue. The sounds are muffled, presumably as the result of a reduction of cardiac output. Arrhythmia of various kinds, including notably auricular fibrillation, as in cases 1

and 6, and prolongation of the P-R interval may be present. The arterial blood pressure is low; the radial pulse is difficult to feel. The diastolic pressure may be unobtainable when the systolic is extremely low. The pulse pressure is reduced. Because the ventricular rate is almost regular the rhythm may be considered as of sinus origin unless an electrocardiogram is taken. The auricular fibrillation seems to last for a number of hours, in 1 case between seven and ten and in another between thirteen and twenty hours.

In the 1 case in which blood was taken for analysis soon after immersion there was found tremendous hyperglycemia and mild hemoconcentration. Examination of blood drawn three days later yielded normal findings.

The temperature falls progressively during the immersion. It appears that a person who continues to wear wet clothing in a cold atmosphere is supercooled to almost the same extent as if he were still immersed in cold water. In case 6 the temperature was 93 F. by rectum one hour after rescue. Presumably it was lower at the time of rescue, but actual determination was prevented by the patient's violent hyperexcitability. In another hour the temperature had risen to 95 F. Within six hours it had reached 100.8 F. It then remained elevated until thirty hours after rescue.

Pyrexia following hypothermia of more than the mildest grade of severity seems to be a constant phenomenon, which persists for many hours. Since the external heat applied to most of the patients was only moderate in amount and was discontinued long before the body temperature returned to normal, it is thought that the fever may be a compensatory phenomenon, representing a specific reaction to hypothermia. The mechanism of this is unknown. It seems possible [3] that it originates in the central nervous system, perhaps in the temperature-regulating center.

The changes in the central nervous system include loss of consciousness, loss of memory and irrational behavior. These clear up as the acute condition subsides, although the period of amnesia may remain.

THERAPY

The treatment used followed the broad general principles applicable for shock. As far as possible, all patients were placed in a superheated room in bed. Wet clothes were removed immediately. The body was dried with warm towels. Warm blankets and hot water bags were

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3. Grosse-Brockhoff, F., and Schoedel, W.: Das Bild der akuten Unterkühlung in Tierexperiment, Arch. f. exper. Path. u. Pharmakol. **201**:417-442 (June 12) 1943; abstracted, Bull. War Med. **4**:508 (May) 1944.

applied.   Light massage of the arms and legs was employed, with doubtful results.   In case 6 the utilization of a heat cradle over the nude body was thought to be a more effective method for the application of external heat than any of the aforementioned methods.

During the course of the six month period when observations were made on the patients in this series, the idea of the desirability of rapid reheating of the body, as contrasted with the generally accepted method of slow rewarming, evolved on an empiric basis.   Rapid rewarming was long ago advocated by Lapchinski[4] and recently substantiated by Russian and German investigators.[5]

Conscious patients were given warm drinks such as tea and coffee in moderate amounts on an empiric basis and with the idea of providing local warmth in the region of the heart.[3]   Whisky and rum were allowed, preferably well diluted with nonalcoholic drinks.   Acute alcoholism was observed in 1 patient who was allowed 4 to 6 ounces (118 to 177 cc.) of rum by a well meaning sickberth attendant.

A total of 4 units of blood plasma (1,600 cc. of fluid) was given intravenously in the course of one and a half hours to the patient in case 6.   He was the most seriously ill of all those encountered.   When he was first seen he appeared moribund.   At the end of one and a half hours of treatment, he had completely recovered consciousness and was feeling well.   It is noteworthy that there was only a small output of urine despite the large intake of fluid.   The experience in this case suggests that the use of blood plasma intravenously may be indicated in immersion hypothermia, as it is in shock.   Theoretic considerations have been offered against administration of plasma in patients who have been cooled for several days (Talbott); but there are differences in the circulatory reactions of persons who are cooled rapidly and in those whose temperatures are kept at a low level.

The use of drugs was avoided in the treatment of these patients. Caffeine and nikethamide are probably not beneficial[6] as stimulants.

4. Lapchinski, F. F.:   Treatment of Frozen Limbs, Vrach., St. Petersb. 87: 119, 1880; abstracted, Zentralbl. f. Chir. 15:228, 1880.

5. (a) Scheiniss, B.:   Death from Exposure to Cold, Moscow, 1943.   (b) Weltz, G. A.; Wendt, H. J., and Ruppin, H.:   Erwärmung nach Lebensdrohender Abkühlung, München. med. Wchnschr. 52:1092, 1942.   (c) Hozlohner, E.; Rascher, S., and Finke, E.:   Bericht über Abkühlungsversuche am Menschen, secret report to H. Himmler, Oct. 16, 1942; translated, Alexander, L.:   Treatment of Shock from Prolonged Exposure to Cold, Washington, D. C., Caducean Press, to be published.

6. Grosse-Brockhoff, F., and Schoedel, W.:   Tierexperimentelle Untersuchungen zur Frage der Therapie bei Unterkühlung, Arch. f. exper. Path. u. Pharmakol. 201:457-467 (June 12), 1943; abstracted, Bull. War Med. 4:508 (May) 1944.

Atropine [7] reduces the vagal effect and elevates the arterial pressure. Intravenous use of dextrose [6] raises the blood pressure and supplies fluid. The use of epinephrine is definitely contraindicated. Grosse-Brockhoff and Schoedel [6] stated the belief that it reduces the arterial pressure in experimentally cooled animals. Rosenblum, Hahn and Levine [8] produced auricular fibrillation experimentally in hyperthyroid animals by amounts of epinephrine insufficient to alter cardiac rhythm ordinarily. Crismon [9] observed that small doses of epinephrine have an effect on cold animals far beyond that resulting in normal animals and that ventricular fibrillation may ensue. Kossman [10] stated that an "epinephrine effect" may occur spontaneously in experimental hypothermia in human beings, i. e., rise of the diastolic blood pressure with concomitant falling systolic pressure. It seems probable that the cooled heart responds abnormally to drugs. Among the reports of cases of immersion available for study [2] there occurred two deaths in which the data, although scanty, seem to confirm this. Each patient had had prolonged immersion during cold weather, 1 for forty-five minutes and 1 for one hundred minutes. Both died seven to nine hours after rescue. The treatment in each case included epinephrine given intravenously.

COMMENT

The clinical picture of immersion hypothermia is in general apparently similar to that of experimentally produced hypothermia. Under experimental conditions [11] the internal temperature of the body may be lowered to 75 F., with subsequent recovery. Changes occur early in the cardiovascular system. There is an initial rise of the pulse rate and arterial blood pressure, with a later fall in both, notable vasoconstriction, both arterial and venous, and increase in the viscosity of the blood. Later the pulse becomes imperceptible, the circulation time is prolonged to two or three times the normal and the blood volume is decreased. The auscultatory findings in the 2 patients with auricular fibrillation

7. Grosse-Brockhoff, F., and Schoedel, W.: Zur Wirkung der Analeptica auf unterkühlete Tiere, Arch. f. exper. Path. u. Pharmakol. **201**:443-453 (June 12) 1943; abstracted, Bull. War Med. **4**:508 (May) 1944; footnote 6.

8. Rosenblum, H.; Hahn, R. G., and Levine, S. A.: Epinephrine: Its Effect on the Cardiac Mechanism in Experimental Hyperthyroidism and Hypothyroidism, Arch. Int. Med. **51**:279-289 (Feb.) 1933.

9. Crismon, J. M.: Third Physical Fitness Conference, Sub-Committee on Clinical Investigation, Report no. 16, Washington, D. C., Oct. 5, 1943.

10. Kossman, C. E., and others: General Crymotherapy: Cardiovascular Aspects, Bull. New York Acad. Med. **16**:317-320 (May) 1940.

11. Talbot, J. H.: The Physiologic and Therapeutic Effects of Hypothermia, New England J. Med. **224**:281-288 (Feb. 13) 1941.

changed decidedly in rate, in rhythm and in type and intensity of the cardiac sounds while under observation. A transient diastolic murmur was heard in case 1. In case 6 a systolic murmur was heard intermittently. It is thought that these changes were caused by transient cardiac dilatation.

Auricular fibrillation and auricular flutter without other evidence of cardiac disease have been described clinically [12] and experimentally.[13] Such arrhythmias appear to be generally benign and are often transient. Cold has not been listed among the inciting factors of the clinical condition, although investigators of experimental hypothermia have encountered it fairly frequently.[14] According to Kossman abnormal rhythm is rare until the temperature drops below 85 F.

Friedlander and Levine [12b] considered benign auricular fibrillation without organic cause to be the result of a "trigger" phenomenon which may be of neurogenic origin. Hyperthyroidism has been cited as an illustrative condition, and epinephrine has been incriminated as the "trigger." Nahum and Hoff [13a] considered that fibrillation is produced by the interaction on the auricular myocardium of two factors: a predominant vagus activity and a specific exciting factor such as thyroxin. They were able to convert the normal cardiac rhythm of 4 hyperthyroid patients into auricular fibrillation by the administration of acetyl-beta-methylcholine. According to Bruenn [15] and Keith,[16] prolongation of the P-R interval in rheumatic heart disease is due to vagal activity. A high degree of correlation between the incidence of partial heart block and auricular fibrillation in various types of cardiac disease and in thyrotoxicosis was found by Altschule.[17] The two conditions occurred alternately in the

12. (*a*) Orgain, E. S.; Wolff, L., and White, P. D.: Uncomplicated Auricular Fibrillation and Auricular Flutter, Arch. Int. Med. **57**:493-513 (March) 1936. (*b*) Friedlander, R. D., and Levine, S. A.: Auricular Fibrillation and Flutter Without Evidence of Organic Heart Disease, New England J. Med. **211**:624-629 (Oct. 4) 1934. (*c*) Fowler, W. M., and Baldridge, C. W.: Auricular Fibrillation as the Only Manifestation of Heart Disease, Am. Heart J. **6**:183-191 (Dec.) 1930.

13. (*a*) Nahum, L. H., and Hoff, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl-B-Methyl-Choline Chloride, with Observations on Role of Vagus and Some Exciting Agents in Genesis of Auricular Fibrillation, J. A. M. A. **105**:254-257 (July 27) 1935. (*b*) Rosenblum, Hahn and Levine.[8]

14. Kossman and others.[10] Talbott.[11]

15. Bruenn, H. G.: Mechanism of Impaired Auriculoventricular Conduction in Acute Rheumatic Fever, Am. Heart J. **13**:413-425 (April) 1937.

16. Keith, J. D.: Overstimulation of Vagus Nerve in Rheumatic Fever, Quart. J. Med. **7**:29-41 (Jan.) 1938.

17. Altschule, M. D.: The Relation Between Vagal Activity and Auricular Fibrillation in Various Clinical Conditions, New England J. Med. **233**:265-266 (Aug. 30) 1945.

same patients, and both were thought to be the consequence of vagal activity. The afferent impulses producing vagal overaction on the heart in disease may arise from the root of the aorta, the great veins or the lungs.[17]

If one may assume that the cardiac arrhythmia of immersion hypothermia is the result of vagal overactivity, it is thought that it may be produced by the local effect of cold on the heart. There may be a specific sensitivity of some persons to cold, which predisposes to cardiac arrhythmia. The amount of sea water swallowed may be a factor. In both cases with auricular fibrillation (cases 1 and 6) there was evidence of a good deal of water being swallowed. That duration of immersion and temperature of the water are not the sole factors is evidenced by the difference between the patients in cases 1 and 2, both of whom were immersed at the same time for approximately the same length of time.

In experimentally induced hypothermia hemoconcentration may occur,[11] with a red blood cell count of 25 per cent above normal, a white blood cell count several times normal, an increase in polymorphonuclear neutrophils and a rise in reticulocytes. In case 6 of this series, comparison of blood removed at half an hour with that removed at seventy-two hours after rescue suggests confirmation of the elevation of the red and white blood cell counts. No explanation for the relative lymphocytosis is offered. Blood was drawn from the rest of the patients too late to be of significance.

The chemical constituents of the blood in experimental hypothermia are said to show little change.[18] The one chemical finding of importance in this series is the remarkably high blood sugar content found at first observation of the patient in case 6 (see previous remarks on the effect of epinephrine). The initial nonprotein nitrogen level in case 6 was moderately elevated.

In the causation of immersion hypothermia there are several emotional factors not found under the conditions of experimental hypothermia. The patients had been flying under constant strain for six to twelve hours, preparing for and engaging in combat and finding their way back to their bases under adverse conditions. In some there was a fear of flying over water. The realization of having to abandon the airplane and of being lost in the open sea, with the necessity of fighting against drowning, added to the emotional problem. The physiologic counterpart of this probably included the outpouring of increased amounts of certain physiologic secretions, including epinephrine.

Subsequent to the first draft of this paper there has been seen the summary of an extraordinary series of experiments, as yet unpublished,

18. Mazer and Sheeley.[2] Talbott.[11]

performed on human beings confined in German concentration camps.[4c] As the result of such experimentation on an allegedly large number of subjects, the German investigators concluded that the curve of rectal temperature of human beings chilled in water at 2 to 12 C. (35.6 to 53.6 F.) dropped slowly to 35 C. (95 F.) and thereafter more rapidly, with death at 27 to 26 C. (80.6 to 78.8 F.). Death was thought to result from cardiac failure, the damage being due to overloading of the heart caused by increase in viscosity of the blood and throttling of peripheral vascular districts. Auricular fibrillation occurred constantly when the rectal temperature dropped below 29 C. (84.2 F.). The prognosis was considered poor when the rate of fibrillation was slow and more favorable when the rate became faster. The blood sugar content rose in inverse proportion to the fall of the temperature. After removal of the patient from the water, the body temperature sank for fifteen minutes or longer. The most effective treatment was heat applied rapidly, best administered by means of immersion in a hot bath (temperature 40 to 50 C. [104 to 122 F.]). Heating by means of a cradle was considered decidedly inferior to immerson in a hot bath as a method of resuscitation but superior to all other methods. Drug therapy was not thought to be advisable. The administration of blood plasma was not discussed. The observations made in case 6, which is the only case in the present series in which the patient was seen immediately after immerson severe enough to produce unconsciousness, appear entirely compatible with the German data.

CONCLUSIONS

1. Immersion hypothermia is a progressive clinical syndrome which may follow immersion in cold water. It is related to experimental hypothermia and to clinical shock.

2. The clinical picture is the resultant of the coldness of the water, the length of the exposure, the emotional factors affecting the patient before and during exposure and the specific response of the person to cold.

3. The chief effects are those on (a) the cardiovascular system (among the transient conditions observed were auricular fibrillation and flutter, ventricular extrasystoles, slight prolongation on the P-R interval and falling arterial blood pressure, with narrowing of the pulse pressure), (b) the nervous system (partial to complete loss of consciousness and irrational behavior were observed) and (c) the blood (hemoconcentration and notable hyperglycemia were found in 1 case).

4. Treatment consists in rapid restoration of normal body temperature by external heat, minimal activity, administration of warm fluids by mouth and, in severe conditions, use of blood plasma. No drugs were used in this series. Use of epinephrine is contraindicated.

SUMMARY

1. Reports of cases are made of 6 patients who suffered from immersion in the North Sea on their return from long combat-flying missions.

2. Four of the patients had transient electrocardiographic abnormalities. One had abnormalities of blood chemistry.

3. The causation and therapy of immersion hypothermia are discussed, and the findings are compared with those in experimental hypothermia.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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(Concluded from Page 769)

STREPTOMYCIN IN SYPHILIS

Herrell and Nichols [196] have treated 4 patients with syphilis with 10,000,000 units of streptomycin given in divided doses over a period of ten days. In 3 cases of early syphilis results were negative at dark field examination after treatment, but in each case clinical relapse was observed. One patient with late gummatous syphilis had "temporary improvement."

Dunham and Rake [197] infected rabbits by the intracutaneous injection of T. pallidum and three days later gave to alternate animals intramuscular injections of streptomycin or crystalline penicillin G. The small amount of streptomycin that cured any of the rabbits when administered in divided doses over a four day period was 79,000 units per kilogram (375 mg. per kilogram) in one experiment and 187,000 units per kilogram (817 mg. per kilogram) in another. Since a comparable effect was obtained with 147 units per kilogram (0.088 mg. per kilogram) of crystalline penicillin G, it is concluded that streptomycin has spirocheticidal action but that penicillin G is more than three thousand times as effective.

FEVER THERAPY

Inoculation Malaria.

Historical.—Of interest to the historian is Bruetsch's [198] translation of Wagner-Jauregg's "The History of the Malaria Treatment of General Paresis." Priority for the use of malaria and relapsing fever in the treatment of dementia paralytica has been claimed [199] for Rosen-

196. Herrell, W. E., and Nichols, D. R.: The Clinical Use of Streptomycin: A Study of Forty-Five Cases, Proc. Staff Meet., Mayo Clin. **20**:449 (Nov. 28) 1945.

197. Dunham, W. B., and Rake, G.: The Activity of Streptomycin in Experimental Syphilis, Science **103**:365 (March 22) 1946.

198. Wagner-Jauregg, J.: The History of the Malaria Treatment of General Paralysis, Comment and Translation by W. L. Bruetsch, Am. J. Psychiat. **102**:577 (March) 1946.

199. Priority in the Discovery of Fever Therapy in Psychoses, editorial, J. A. M. A. **124**:1061 (April 8) 1944.

blium. According to Wagner-Jauregg, however, "The facts, however, are that Rosenblium has never inoculated his patients with the idea of treating their mental illness. What he did was to make available his mental patients—among whom were no general paralytics—to the bacteriologist Motschutkoffsky, who in Odessa in the year of 1876 studied the transmissibility of recurrent fever to human beings. Subsequently, a few of these patients recovered from their psychoses and Rosenblium reported this later under an assumed name."[200]

Wagner-Jauregg, whose great contribution to syphilotherapy won him the Nobel Prize in 1927, acknowledges that the first suggestion to treat patients with mental disease with malaria was made in 1876 by Raggi,[201] who never put his idea into practice. Even earlier, indirect malaria therapy had been carried out by Galloni, director of an Italian institution for mental disease, who withheld quinine from psychotic patients who incidentally had contracted malaria, as he observed that such patients with mental disease frequently recovered from their psychoses.

The Clinical Aspects of Inoculation Malaria.—The clinical characteristics of the paroxysm from therapeutic infections with the McCoy strain of P. vivax are described by Kitchen and Putnam.[202] According to these investigators, the onset of therapeutic malaria may be characterized by a few days of continuous-remittent or quotidian or tertian intermittent fever, but, regardless of the type of onset, most therapeutic P. vivax attacks settle into quotidian periodicity. Among fifty-one attacks in this series, only one was tertian in character throughout. For some unexplained reason, the parasites are divided into two broods, whose maturation and sporulation times were separated by approximately twenty-four hours, thus creating quotidian activity. The behavior of the two cycles characterizing quotidian activity was similar with respect to all factors studied. The presence of rigor appeared to be an index of the severity of the paroxysms. The mean maximum temperature observed was 104.2 F. for six hundred and fifty-four paroxysms with rigor, while that for three hundred and forty-six rigorless paroxysms was 102.5 F. The maximum observed temperature being used as the marking point, two thirds of the paroxysms occurred between 3 and 8 p.m., thus disproving a common belief that malaria paroxysms occur chiefly during the morning. The authors state the belief that a change occurs in the host-parasite relationship at about the end of the first week of the attack.

200. Oks, B.: Ueber die Wirkung fieberhafter Krankheiten auf Heilung von Psychosen, Arch. f. Psychiat. **10**:249, 1880.

201. Raggi, A.: Il processo febbrile nei pazzi, Riv.clin.di Bologna **6**:163, 1876.

202. Kitchen, S. F., and Putnam, P.: Observations on the Character of the Paroxysm in Vivax Malaria, J. Nat. Malaria Soc. **5**:57 (March) 1946.

Patients vary in their susceptibility to therapeutic malaria. These variations in susceptibility have been studied by Becker and his associates,[203] who have treated 300 patients in the United States Army for neurosyphilis, utilizing inoculation malaria. Their study corroborates the generally accepted opinion that Negroes and patients from the Mediterranean area are refractory to inoculation with P. vivax. It also was found that patients from endemic areas in Puerto Rico and the southeastern United States who have a history of malaria usually are less responsive to the tertian infection. Of the white patients, 208 were inoculated with P. vivax and 185 (90 per cent) had a satisfactory therapeutic course of ten or more paroxysms following primary inoculation. Some malaria therapeutists have been reluctant to inoculate natives of the southeastern United States with tertian malaria. Included in the present study were 43 white patients from this area, 80 per cent of whom proved to be susceptible. Of the 11 patients in whom the results were failures, all but 1 had had chills and fever at some time. Of those from the remainder of the United States, 93 per cent were satisfactorily treated with P. vivax.

Daily determination of the degree of parasitemia was found helpful in following the course of the infection as to its severity, degree of the patient's resistance and early forecasting of an immune response.

The problem of giving adequate malarial therapy to white patients with neurosyphilis who are partially immune to P. vivax infections is a provoking one. In order to complete a course of therapeutically effective malaria, reinoculations often are necessary. There are two objections to reinoculation with quartan malaria: (1) quartan reinoculation prolongs hospitalization because of the prolonged incubation period and the longer duration of the cycle, and (2) quartan infections not infrequently recur following antimalarial therapy. To study the problem, Kaplan, Read and Becker [204] made a cross inoculation study of malaria strain immunity with homologous and heterologous strains of P. vivax. Reinoculations with homologous strains produced minimal clinical activity. The duration of the homologous reinfection in this series of patients averaged 10.5 per cent of the duration of the original infection with the same strain. With heterologous strains of P. vivax (i. e., those differing in geographic origin from the original strain), reinoculation oftener produced therapeutically significant paroxysms. In the cross inoculation study, the duration of the heterologous reinfection averaged 74.3 per cent of the duration of the original infection. These authors

203. Becker, F. T.; Kaplan, L. I.; Read, H. S., and Boyd, M. F.: Variations in Susceptibility to Therapeutic Malaria, Am. J. M. Sc. **211**:680 (June) 1946.

204. Kaplan, L. I.; Read, H. S., and Becker, F. T.: Homologous and Heterologous Strains of Plasmodium Vivax: A Cross-Inoculation Study of Malaria Strain Immunity, J. Lab. & Clin. Med. **31**:400 (April) 1946.

state the belief that it is desirable to reinoculate with heterologous strains of P. vivax the white patients with neurosyphilis who prove to be partially immune to the originally inoculated strain. Completion of adequate courses of fever therapy without the use of quartan infections thus may be accomplished.

In most patients with active malarial infections there develop anemia and hypoproteinemia. Anemia usually is considered to be secondary to erythrocyte destruction, but no adequate explanation has been offered for hypoproteinemia. Feldman and Murphy [205] have studied the changes in blood volume associated with active untreated malaria to determine alterations in the total plasma protein contents and in the number of red blood cells. Simultaneous determinations of the plasma protein levels, plasma bilirubin level and erythrocyte concentrations were made so that the relative and total amounts might be calculated and compared. Blood plasma volume was found to be increased during the active phase of P. vivax and Plasmodium falciparum infections, reflecting the ability of the body to maintain a fairly constant blood volume in the presence of erythrocyte destruction. The increased plasma volume was disproportionately great after a paroxysm, thus exaggerating the degree of anemia. The calculated mass of circulating erythrocytes progressively decreased during P. vivax and P. falciparum infections and was in relation to an increase in plasma bilirubin levels.

Feldman and Murphy conclude that the normocytic anemia of clinically active malaria may be due to the two factors of erythrocyte destruction and hemodilution. The concentration of plasma proteins falls during the clinical phase of the disease, but the total amount of circulating plasma protein remains fairly constant.

Another explanation for at least part of the anemia and leukopenia so often observed in the course of therapeutic malaria is offered by Lanza.[206] In a study of the sternal marrow cellular components of 15 patients with acute malaria, this investigator found increases in the reticuloendothelial cells and in the plasma cells, regressive changes in the cells of the granulocytic series and an erythroblastic reaction proportional to the degree of anemia. These myelotoxic phenomena he believes are of significance in the genesis of malarial anemia and leukopenia.

Complications of Malarial Therapy.—The complications encountered in a series of 300 patients with neurosyphilis treated with therapeutic

205. Feldman, H. A., and Murphy, F. D.: The Effects of Alterations in Blood Volume on the Anemia and Hypoproteinemia of Human Malaria, J. Clin. Investigation **24**:780 (Nov.) 1945.

206. Lanza, G.: Citologia del midollo osseo nella malaria acuta, Pathologica **36**:31, 1944.

malaria are analyzed by Read and his co-workers,[207] who express the opinion that the more usual clinical features of malaria, i. e., anemia, lowered blood pressure, herpes simplex, gastrointestinal discomfort, muscular pain, cough and loss of weight should not be considered "complications."

Jaundice, edema, mild renal damage and peripheral neuropathy were encountered most frequently. Although these complications posed certain therapeutic problems, none was followed by permanent sequelae. Excessive red blood cell hemolysis in the absence of impaired hepatic function accounted for approximately 50 per cent of the cases of jaundice. Infectious hepatitis, serum jaundice and toxic hepatitis also were considered causes of this complication.

The precipitating cause of edema during active malaria oftenest was hypoalbuminemia, although 3 cases of unexplained edema were noted. Albuminuria and microscopic hematuria occurred frequently and were benign. Four cases of acute nephritis, supposedly due to the malaria parasite, were encountered. Three of the 4 patients received therapeutic quartan malaria, and the complication oftenest occurred prior to the fifth paroxysm. Two patients were classified as having diffuse glomerulonephritis, and 2 were considered to have focal embolic glomerulonephritis. The observed neuropsychiatric manifestations of P. vivax and Plasmodium malariae malaria were benign and readily amenable to antimalarial therapy. Two mental complications, one an agitated psychosis and the other an acute hallucinatory syndrome, may have been related to therapy with quinacrine hydrochloride (atabrine). In 13 patients there developed respiratory difficulty not due to pneumonitis. Severe and unexplained respiratory distress with cyanosis was observed in 2 cases. Bronchial asthma was decidedly aggravated during malarial paroxysms. Such unusual complications as perisplenitis, purpura, herpes zoster, urticaria, hyperlipemia, auricular fibrillation, spontaneous rupture of the spleen and hypocalcemic tetany are described briefly. In this series of 300 patients treated with benign tertian and quartan malaria there were two deaths, one due to rupture of the spleen and one to hypocalcemic tetany.

The medical literature contains many references to a variety of untoward effects of malaria on the cardiovascular system. Of the characteristics of malaria which might be expected to affect the heart are its chronic and recurrent nature, the systemic toxemia of the paroxysm, the anemia which is induced and occlusion of capillaries and arterioles in the coronary circulation.

207. Read, H. S.; Kaplan, L. I.; Becker, F. T., and Boyd, M. F.: An Analysis of Complications Encountered During Therapeutic Malaria, Ann. Int. Med. 24:444 (March) 1946.

Sprague's [208] experience during World War II indicates that malaria rarely causes cardiovascular damage. In none of several thousand cases of malaria did he observe any cardiac condition which could be specifically attributed to malaria. Any chronic disease, especially one resulting in anemia, may produce tachycardia, premature systoles or functional systolic murmurs, and malaria is no exception. A series of 50 cases of recurrent malaria, in all but 1 of which the condition was due to P. vivax, were studied electrocardiographically. Among the entire group there was no finding which could be considered outside the range of normal variation or of specific import. There were no deaths from acute cardiac disease or any proved chronic cardiac disease in this series. One would expect none, therefore, from therapy with inoculation malaria.

Grant [209] states the belief that malaria may incite several characteristic disturbances in various parts of the eye. The complications encountered, though mostly monocular, may be moderately incapacitating. The most frequent ocular condition encountered is herpetic keratitis, a nonspecific lesion. Lesions of the choroid, retina and optic nerve, which from histopathologic evidence appear to be due to emboli of parasitized red blood cells and which commonly are bilateral, appear to be the most serious of the complications from the standpoint of interference with vision. Results of treatment of these ocular disturbances with antimalarial drugs usually are successful, except in the case of herpetic keratitis, a virus disease for which specific chemotherapy is not available.

Bronstein and Reid [210] have been unable to confirm a previous report that all patients with malaria have abnormal hepatic function as measured by the cephalin-cholesterol flocculation test. They did find, however, indications of impaired hepatic function in approximately 75 per cent of the patients with malaria studied.

Cook and Hoffbauer,[211] who have studied hepatic function in 12 patients with therapeutic malaria before, during and after malaria therapy, also confirm the observation that there occurs transient but reasonably constant and readily detectable impairment of hepatic function. Four laboratory tests were used: the cephalin-cholesterol flocculation test, quantitative serum bilirubin test, quantitative Ehrlich reaction

208. Sprague, H. B.: The Effects of Malaria on the Heart, Am. Heart J. **31**:426 (April) 1946.

209. Grant, W. M.: Ocular Complications of Malaria, Arch. Ophth. **35**:48 (Jan.) 1946.

210. Bronstein, L. H., and Reid, R. D.: The Cephalin-Cholesterol Flocculation Test in Malaria, Proc. Soc. Exper. Biol. & Med. **31**:56 (Jan.) 1946.

211. Cook, C. D., and Hoffbauer, F. W.: Liver Functional Impairment in Therapeutic Malaria with Particular Reference to the Unsuccessful Use of Methionine as a Protective Agent, J. Lab. & Clin. Med. **31**:56 (Jan.) 1946.

and sulfobromophthalein test. Alternate patients, 6 of the 12, were given 8.1 Gm. of methionine orally per day in addition to a general diet. All 12 of the patients studied exhibited some evidence of disturbed hepatic function by one or more of the tests used. In 10 of the subjects, the abnormalities persisted from one to three days after the termination of the malaria. The addition of methionine to the diet failed to protect the liver.

Possibly the most spectacular major complication of malarial therapy, and certainly one of the most serious, is spontaneous rupture of the spleen. This accident, which, fortunately, is rare, has in the past invariably resulted in death. Moses,[212] however, has recorded a case in which early recognition of the condition and prompt surgical intervention resulted in recovery.

That acute psychoses of the paranoid type may follow therapeutic malaria is noted by Kaplan and his co-workers,[213] who have observed this complication of malarial therapy in a patient treated for apparently asymptomatic neurosyphilis. The problem of nonsyphilitic mental complications in patients with neurosyphilis is discussed, and it is indicated that considerable diagnostic confusion may arise when an attempt is made to differentiate syphilitic from nonsyphilitic psychoses in patients with positive cerebrospinal fluids, especially those treated with malaria.

Kitchen and Sadler [214] have reported that in a patient with dementia paralytica treated with inoculation malaria there developed an episode of blackwater fever. The attack lasted one week and was characterized by anemia, emesis, daily afternoon fever, hemoglobinemia, hemoglobinuria, proteinuria, bilirubinemia, icterus and near collapse. It is notable that this patient had been inoculated not only with P. vivax and P. malariae but, in an effort to obtain a satisfactory course of fever, with P. falciparum as well and that the parasites of malignant tertian malaria were known to have been present intermittently in the blood for a period of five months prior to the onset of hemoglobinuria. Had the original intention been to produce blackwater fever experimentally, it is doubtful whether a more satisfactory method could have been utilized.

Public Health Aspects of Inoculation Malaria.—From time to time there has been an uneasiness in public health circles that new foci for malaria epidemics may be created by the therapeutic inoculation of neurosyphilitic patients. However, after extensive study of the sub-

212. Moses, W. R.: Splenic Rupture in Therapeutic Malaria, South. M. J. **38**:745 (Nov.) 1945.

213. Kaplan, L. I.; Flicker, D. J.; Becker, F. T., and Read, H. S.: Acute Psychosis Following Therapeutic Malaria in a Case of Neurosyphilis, J. Nerv. & Ment. Dis. **102**:285 (Sept.) 1945.

214. Kitchen, S. F., and Sadler, G. G.: Report of an Attack of Blackwater Fever Subsequent to Induced Malaria, Am. J. Trop. Med. **25**:379 (Sept.) 1945.

ject, Bruetsch[215] concludes that, although there exists the theoretic possibility of accidental transmission of malaria from an artificially inoculated patient, malaria therapy, if properly managed, is not a practical menace to the public health. A critical review of the cases of malaria alleged to have originated from inoculation malaria indicates a lack of definite proof in almost all cases. The theory that the maintenance of malaria in the human host for prolonged periods by direct person to person inoculation leads to asexualization of the plasmodium is rejected in favor of the belief that unfavorable ecologic requirements adequately explain why accidental transmission practically never occurs.

Artificial Fever.

The Chicago Intensive Treatment Center group has further described the technic used by them for the administration of therapeutic fever by means of the hypertherm.

Craig, Buroker and Schwemlein[216] have discussed in detail the management of patients during the "induction period," stressing careful thermometry and the use of oxygen, fluids and sedation. During the induction period, the nurse-technician must be constantly alert for signs of cardiac or respiratory embarrassment and must keep close check on urinary function. The induction period ends when the rectal temperature reaches 105.8 F. if the desired temperature level is 106 F.

Describing the "maintenance" period of artificial fever therapy, Schwemlein, Buroker and Craig[217] note that the stabilization of the patient's temperature at the desired level is difficult, considerable experience being required to prevent "overshooting." In their experience, leveling of the patient's body temperature depends largely on the factors of skill of the nurse-technician, climatic conditions in the fever department, cabinet air temperature during the induction period, relative humidity of the cabinet air, induction period, weight of the patient, physiologic pattern (sic) and muscular activity of the patient.

Fever from Typhoid Pyrogens.

A purified pyrogenic antigen isolated from cultures of Eberthella typhosa has been found by Favorite and Morgan[218] to be a reliable

215. Bruetsch, W. L.: The Public Health Aspect of Malaria Therapy of Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **29**:494 (Sept.) 1945.

216. Craig, R. M.; Buroker, F. M., and Schwemlein, G. X.: Artificial Fever-Chemotherapy: V. Induction Period, Arch. Phys. Med. **26**:582 (Sept.) 1945.

217. Schwemlein, G. H.; Buroker, F. M., and Craig, R. M.: Artificial Fever-Chemotherapy: VI. Maintenance Period, Arch. Phys. Med. **26**:623 (Oct.) 1945.

218. Favorite, G. O., and Morgan, H. R.: Therapeutic Induction of Fever and Leucocytosis Using a Purified Typhoid Pyrogen, J. Lab. & Clin. Med. **31**:672 (June) 1946.

substance for the induction of therapeutic fever. These writers state the belief that the stability and uniformity of this pyrogen and its effectiveness in small single doses make it preferable to the whole typhoid-paratyphoid vaccine now commonly used. Temperature of from 103 to 105 F. followed the intravenous injection of from 0.001 to 0.002 mg. of this substance, but to obtain similar results with subsequent injections the amount of the pyrogen had to be increased threefold to fivefold.

Results of Fever Therapy.

From the careful histopathologic study of the visual pathways of 70 patients with all types of syphilis of the central nervous system, Bruetsch[219] deduces that the beneficial effects of malaria therapy in the control of syphilitic optic atrophy can best be explained on the basis that the degeneration of the optic nerves is due to a chronic inflammatory process which is arrested by malaria treatment. Despite clinical observation that primary optic atrophy is oftener observed in association with tabes dorsalis than with dementia paralytica, Bruetsch insists that the pathologic basis of the condition is more like that of paralysis (chronic inflammation) than that of tabes (degeneration). In his opinion, the reason that optic atrophy is not oftener observed in association with paralysis is that if untreated the latter is usually fatal before the ocular lesion has time to develop. Bruetsch finds malaria therapy more effective than mechanical hyperpyrexia in the treatment of optic atrophy, since he states the belief that he has found evidence that the "activation of the mesodermal tissue," which is produced by the malaria plasdomia and not by the elevated temperature, is responsible for the cessation of the inflammatory reaction. In view of the recent fad for surgical intervention to release adhesions resulting from optochiasmatic arachnoiditis, it is of note that this study indicates that in the majority of cases of syphilitic optic atrophy adhesive optochiasmatic arachnoiditis plays no part in the development or progress of the atrophy.

Lascara,[220] who has used both artificial fever and inoculation malaria in the treatment of neurosyphilis at the Central State Hospital, Petersburg, Va., favors artificial fever because, he states:

(a) The patients tolerate artificial fever therapy more readily; (b) patients can be treated on an ambulatory basis; (c) treatment complications are minimized; (d) the risks of inoculating an already ill patient with another infectious disease (malaria) are eliminated.

219. Bruetsch, W. L.: Malaria Therapy in Syphilitic Optic Atrophy, J. A. M. A. **130**:14 (Jan. 5) 1946.

220. Lascara, V. E.: Neurosyphilis with a Three Year Observation of the Comparative Therapeutic Effects of Inoculation Malaria and Artificial Fever Therapy, Virginia M. Monthly **73**:111 (March) 1946.

This author, whose findings are at variance with most previous reports, states that 84 per cent of the patients treated with artificial fever were improved, whereas only 48 per cent of the malaria-treated patients were benefited. In three months his mortality rate from artificial fever was 3 per cent and from inoculation malaria an amazingly high 22 per cent.

Knight and Schachat[221] summarize their experience with hyperthermia in the treatment of various syphilitic lesions of the eye. Fever therapy was supplemented with chemotherapy and the usual local ophthalmic therapeutic measures. Among 19 cases of primary optic atrophy, improvement was noted in 4 and clinical arrest of symptoms in 7. In the treatment of syphilitic choroiditis, the method was valuable, especially when the lesions were recent. Excellent results were obtained in 6 cases of acute iritis associated with secondary syphilis and in 4 cases of interstitial keratitis.

FEVER AS AN ADJUNCT TO PENICILLIN OR TO METAL CHEMOTHERAPY

In view of proposals to combine fever with metal chemotherapy or penicillin, a review by Fuhrman[222] on the effects of body temperature on drug action in general is timely. The effects of temperature on the action of drugs should be interpreted as to the rate, intensity and duration of action. The rate of action is determined by the time required for a drug to reach the site of action in sufficient concentration to produce its effect and by the time required for the interaction between the drug and (for example) a pathogenic organism. The time between administration and the appearance of effect is greatly influenced by the route of administration. Following intravenous administration, the effect of temperature is a result of the influence of fever on circulation time. Following subcutaneous or intramuscular injection, the rate of absorption is dependent on blood flow in the region of injection. The intensity of drug action largely depends on the concentration of the drug at its site of action, and this concentration in turn is the resultant of the processes of absorption, excretion and destruction within the body. All these processes may be influenced by changes in body temperature. Changes in toxicity (in terms of lethal dose) with changes in temperature may result from effects of fever on either the rate of absorption or the rate of elimination.

Oxophenarsine hydrochloride administered during fever is known to be more effective than is the same amount of the drug given in the

221. Knight, H. C., and Schachat, W. S.: Hyperpyrexia in Treatment of Ocular Conditions Due to Syphilis, Arch. Ophth. **35**:271 (March) 1946.

222. Fuhrman, F. A.: The Effect of Body Temperature on Drug Action, Physiol. Rev. **26**:247 (April) 1946.

absence of fever. One of the objections to combining fever therapy with this drug in the treatment of syphilis has been the lack of data as to how the toxicity of the arsenical is altered by fever. Boak, Dorn and Carpenter [223] have studied the effect of fever on the toxicity of oxophenarsine hydrochloride in rabbits. Their results, expressed in terms of maximal tolerated dose (MTD) and minimal lethal dose (MLD), indicate that the toxicity of the drug for rabbits is significantly increased by the combination. The maximum tolerated dose of oxophenarsine hydrochloride alone for rabbits, observed in this study to be 12 mg. per kilogram of body weight, approximates closely the mean of previous investigators. The reported figure for the minimal lethal dose (16 mg. per kilogram) is lower than the mean of previous studies. When oxophenarsine hydrochloride was injected either before or after physically induced fever, the maximal tolerated dose and the minimal lethal dose were lower than when the drug alone was administered. At the termination of the fever it was less toxic than when given immediately before fever. An increase in the length of the fever from three to five hours after the administration of the drug caused a further increase in toxicity. The weight and age of the animals appeared to influence the results, older and larger rabbits seeming more susceptible to the toxic actions of combined arsenofever therapy.

In 1944, Eagle and Musselman [224] showed that the spirocheticidal action of penicillin increases with the body temperature. Similar effects of hyperthermia on the bactericidal action of penicillin have more recently been reported by Hoyt, Pratt and Levine [225] and by Lee and Foley,[226] both of whom find the in vitro activity of pencillin against Staph. aureus to be enhanced at temperatures above 37 C.

Craig, Schwemlein and Kendell [227] report 20 cases of early syphilis treated with fever combined with penicillin. The amount of fever for each patient was three hours at 106 F., produced in an air-conditioned cabinet (hypertherm). The sodium salt of penicillin was administered prior to and during the course of the fever. Ten patients received

223. Boak, R. A.; Dorn, F. L., and Carpenter, C. M.: The Effect of Fever on the Toxicity of Mapharsen in Rabbits, Am. J. Syph., Gonor. & Ven. Dis. 29:428 (July) 1945.

224. Eagle, H., and Musselman, A. D.: The Spirocheticidal Action of Penicillin in Vitro and Its Temperature Coefficient, J. Exper. Med. 80:493 (Dec.) 1944.

225. Hoyt, R. E.; Pratt, O. B., and Levine, M. G.: The Activity of Penicillin at Temperatures Above 37 C., J. Lab. & Clin. Med. 30:736 (Sept.) 1945.

226. Lee, S. W., and Foley, E. J.: Effect of Temperature on the Action of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. 60:133 (Oct.) 1945.

227. Craig, R. M.; Schwemlein, G. X., and Kendell, H. W.: Penicillin Combined with Fever Therapy: A Preliminary Report of Twenty Cases of Early Syphilis, J. Lab. & Clin. Med. 30:1016 (Dec.) 1945.

300,000 units of penicillin in divided doses during the twenty-four hours of the prefever period and 300,000 units in divided doses during the fever, a total of 600,000 units. In 8 of these 10, results of treatment were failures (five clinical relapses, one clinical progression and two serologic relapses). Ten other patients received 600,000 units of penicillin before and 600,000 units during fever, a total of 1,200,000 units. Among these patients, the results of treatment in 2 were failures (both serologic relapses). The authors express the opinion that they have demonstrated that penicillin and physically induced fever may be safely combined in the treatment of early syphilis, that this form of therapy is less discomforting to the patients than arsenobismuth-fever therapy and that the results are "encouraging enough to warrant further study."

SYPHILIS IN THE POSTWAR WORLD

The available epidemiologic information indicates that the remarkable progress made in the control of syphilis in Europe during the interwar period has been wiped out completely since the beginning of World War II. It has been estimated [228] that syphilis in Europe increased tenfold during the war years. The only reliable indexes of the extent of the increase are those of the Scandinavian countries. In Norway, there appears to have been a sixfold increase in the incidence of syphilis since 1940, while in Denmark an eightfold increase is estimated. In such a predominately maritime nation as Norway, there are, as Guthe [229] notes, two important aspects of the problem: the problems of seamen exposed to the vicissitudes of a war-torn world and the complications engendered by German occupation. The incidence of syphilis in Sweden did not begin to rise until 1942, but since then the increase has ben accelerated.

In Germany, available data [230] suggest that the incidence of syphilis is nearly three times as high as that in Norway and Denmark. This is not surprising, since the licentiousness encouraged by Hitlerite Germany might well be expected to increase the incidence of venereal disease. Data from Switzerland [231] and from Greece [232] and unofficial reports

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228. Rapid Increase of Syphilis in Europe, Epidemiol. Inform. Bull. **1**:403 (June 30) 1945.

229. Guthe, T.: Venereal Disease Control in Europe with Particular Reference to the Scandinavian Countries During World War II, Am. J. Syph., Gonor. & Ven. Dis. **29**:381 (July) 1945.

230. Venereal Disease in Occupied Germany, Epidemiol. Inform. Bull. **1**:801 (Nov. 15) 1945.

231. Pautrier, L. M., and Ullmo, A.: Récrudescence inquiétante de la syphilis dans le canton de Vaud et lacunes dans l'organisation de la lutte antivénérienne en Suisse, Dermatologica **92**:1, 1945.

232. Public Health in Greece During War and Occupation, Epidemiol. Inform. Bull. **1**:885 (Dec. 15) 1945.

from France, Belgium and Italy suggest that during the war years the incidence of syphilis increased significantly throughout the entire European continent.

Also to Soviet Russia,[233] where considerable success reportedly had resulted from a "planned" attack on venereal infections instituted by the Soviet regimen, hardships and mass migrations of war brought an increased incidence of venereal infection.

In the United States, trends toward an increased incidence of syphilis have been reasonably well held in check by intensified programs of civilian and military control. From an analysis of the results of blood tests taken during examination of men for the draft, Usilton[234] concludes that so far as the incidence of syphilis in the United States is reflected in the occurrence of positive serologic reactions among young men, in no section of the country was there any significant increase in the incidence of syphilis between January 1942 and July 1943, a period during which the war effort was expanding rapidly.

There has been an impression that during the recent years of war syphilitic infections among teen-age groups have constituted an increasing proportion of the problem of control of venereal disease. Seeking valid information on the point, Heller[235] has analyzed statistically data concerning patients admitted to public clinics for early syphilis from 1941 through 1944. The analysis was limited to women, since male admissions to clinics during this period were influenced by the war. The study indicates that a shift into the teen ages has not been nationwide, nor has it been constant from one year to another. Moreover, the areas affected were not the same for white persons and Negroes. Considering certain factors as possible causes for this disparity, the author found a tendency toward an earlier age of infection among white women in the presence of an increasing civilian population, particularly in areas of war-boom industrial concentrations. Increasing military populations seemed to have little or no tendency to be associated with an increased proportion of infections among teen-age white girls, presumably because of active control measures within the Armed Forces.

Postwar Syphilis Control.

The postwar problems of syphilis control in the United States have been carefully considered by the United States Public Health Service. The most immediate needs have been studied, and at a meeting of the state and territorial health officers the following recommenda-

233. Mashkilleison, L. M., and Rakhmanov, V. A.: Venereal Disease Control in the USSR, Am. Rev. Soviet Med. **3**:100 (Dec.) 1945.

234. Usilton, L. J.: Syphilis Among Civilians During World War II, January 1, 1942, Through June 30, 1943, J. Ven. Dis. Inform. **26**:263 (Dec.) 1945.

235. Heller, J. R., Jr.: Wartime Changes in the Age Distribution of Females Infected with Syphilis, Am. J. Pub. Health **36**:501 (May) 1946.

tions [236] were made: (1) that efforts be intensified to obtain increased cooperation of private physicians in control of venereal disease; (2) that new educational technics be devised and that a wider use of educational methods be made; (3) that the United States Public Health Service sponsor formal college training courses for investigators of venereal disease, to meet the serious lack of trained personnel; (4) that an evaluation of the present costs of performance of outpatient clinics be made, and (5) that the Rapid Treatment Center Program be made a permanent part of the general program and that inpatient care be extended to all syphilitic patients potentially responsive to intensive therapy, provided that this does not necessitate any curtailment of activity directed toward the control of infectious conditions.

The progress thus far made in implementing these recommendations is described by Heller.[237] Increased cooperation of private physicians has been sought by editorials in the *Journal of Venereal Disease Information* and by urging physicians to give increased attention to reporting cases and to accept the assistance of trained personnel from local health departments in obtaining and following up contact information.

Educational technics are being devised and extended chiefly through the work carried on at the Venereal Disease Educational Institute at Raleigh, N. C. The technics of mass education for intensive short time programs have been further developed. Plans are under way for three to nine month training courses for investigators of venereal disease. The development of inpatient rapid treatment centers lifted a good deal of the treatment burden from many outpatient clinics. An analysis of the costs and functions of clinics is in progress.

The Rapid Treatment Center Program, originally a temporary measure to prevent the spread of venereal disease among military personnel, has been continued. There now are over fifty centers operating throughout the country. In some instances in which it has been impracticable to build new centers, bed space in already existing hospital facilities has been rented.

The release from military service of millions of men might be expected to complicate the problems of civilian control of venereal disease. To minimize these complications, the Army [238] and Navy [239] have

236. Heller, J. R., Jr.: State and Territorial Health Officers Consider the Problem of Venereal Disease Control, J. Ven. Dis. Inform. 26:168 (Aug.) 1945.

237. Heller, J. R., Jr.: The Postwar Syphilis Control Problem in the United States, J. Social Hyg. 31:536 (Nov.) 1945.

238. Sternberg, T. H.: The Army Separation Process, J. Social Hyg. 31:532 (Nov.) 1945.

239. Ferree, J. W., and Ennes, H.: The Venereal Disease Heritage of World War II: A Navy View of Demobilization and Postwar Venereal Disease and Social Hygiene Problems, J. Social Hyg. 31:515 (Nov.) 1945.

instituted at their respective separation centers the following procedures: 1. All separatees are examined for evidence of venereal infection at the time of the final physical examination at separation. 2. Those with infectious or complicated venereal infections are retained in the service and treated until cured or noninfectious. 3. Serologic tests for syphilis are performed at the time of separation to detect cases of latent syphilis. The results of this test are reported to the United States Public Health Service, which via the state health departments notifies the veteran that further diagnostic studies should be carried out and, if necessary, antisyphilitic treatment instituted. Also, information concerning military and naval personnel who have been treated for syphilis while in service but who require further observation is furnished by the Army and Navy to the United States Public Health Service, which in turn forwards this information to the appropriate state health department.

VENEREAL DISEASE EDUCATION

In a report based on three years' study, a special advisory committee to the United States Public Health Service [240] outlines the general principles which should govern public education in control of venereal disease. Three of the committee's findings stand out: 1. Venereal disease education is a primary responsibility of official health agencies and should be conducted by them on an intensive but sustained basis. 2. Whenever possible, this education should be coordinated with other health education programs and so organized as to permit the active participation of interested groups and individuals within the community. 3. There should be a considerable expansion of facilities for training health department personnel who are to engage in venereal disease education, case finding and related activities.

Throughout World War II the Army had an unprecedented opportunity to study the results of the mass use of compulsory education in venereal disease. Larimore and Sternberg [241] describe the technics used and delineate their experiences and results. The aims of the Army's program were to impart technical knowledge about the venereal infections and to motivate the soldier to utilize this information at the time it is needed. Certain principles were found to be essential for the successful use of education as a part of the program for control of venereal

240. Report of U. S. Public Health Service Advisory Committee on Public Education for the Prevention of Venereal Diseases, J. Ven. Dis. Inform. **26**:256 (Dec.) 1945.

241. Larimore, G. W., and Sternberg, T. H.: Does Health Education Prevent Venereal Disease? The Army's Experience with 8,000,000 Men, Am. J. Pub. Health **35**:799 (Aug.) 1945.

disease: an integrated program; best possible quality and attractiveness of all educational materials; abandonment of the pedagogic concept of health education, with the substitution of an approach of "health advertising"; avoidance of overemphasis on sex, and technical accuracy of all educational materials. In motivation of a person to utilize the knowledge he has been given, fear, intelligence, pride and patriotism were found to be efficacious as appeals. Among the reasons for failure are listed the nature of the sex urge itself, sexy motion pictures, advertisements and illustrations, "war psychology," displacement of normal family and social relationships, newer methods of treatment, intemperate use of alcohol and low morale.

In measuring the results of the Army's educational program, the authors believe that the best single criterion is the extent to which prophylactic facilities are utilized. In November 1944, the Army required more than fifty million individual prophylactic items monthly. The utilization of this large number of prophylactics by an Army of eight million men is presumed to indicate favorable results from the educational program.

The results of an experiment in venereal disease education in Negro schools have been described by Carpenter and his fellow educators.[242] A preliminary survey of the knowledge on venereal disease possessed by students in seven Negro schools, comprising one thousand, one hundred and nineteen pupils ranging in age from 12 to 18 years, revealed an appalling lack of accurate information. Discussions with school instructors also revealed a lamentable paucity of factual information in the teacher group. As an informational device among Negro students, class discussion based on accurate information resulted in better learning than did the use of pamphlets and posters alone. All methods of approach used, however, resulted in a pronounced increase in the amount of information, although valid comparisons of the various teaching devices were not possible. It is of significance that there were no objections or criticisms encountered in this program to disseminate information on venereal disease to Negro students in junior and senior high schools.

Koch, Arnstein and Painter [243] discuss their experiences in industrial control of venereal disease in the San Francisco area.

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242. Carpenter, C. M.; Rahm, E.; Kirkendall, L. A., and Winchester, M. E.: An Experiment in Venereal Disease Education in Negro Schools, Am. J. Syph., Gonor. & Ven. Dis. **29**:392 (July) 1945.

243. Koch, R. A.; Arnstein, L., and Painter, A. C.: San Francisco Industrial Venereal Disease Educational and Case-Finding Program, J. Ven. Dis. Inform. **27**:9 (Jan.) 1946.

OTHER ASPECTS OF CONTROL OF SYPHILIS

A unique Alabama law requiring all persons between the ages of 14 and 50 to have serologic tests for syphilis has provided Denison and Smith [244] with the opportunity of observing the results of a short term, intensive campaign of case finding. After an extensive campaign of publicity and mass education and the establishment of suitable laboratory and treatment facilities, approximately 275,000 persons in Birmingham, Ala., were tested in a six week period. From among a population of 480,000, there were uncovered 569 patients with previously unknown early syphilis, 70 per cent of which was in women. The cost of each patient with syphilis found and treated was between $30 and $40. The authors state the belief that such short term case-finding campaigns are helpful in reducing the current mass of infectious venereal disease and that the procedure is practicable for the communities in which the rate of infection is high and in which adequate facilities for treatment and follow-up exist.

The usual contact interview has two objectives: (1) the general education of the patient regarding the disease, its prognosis, necessary treatment and the public health aspects and (2) following directly from the education regarding the public health aspects, the attempt to obtain identifying information about persons who may be infected through contact with the patient being interviewed. An attempt has been made by Hazlehurst, Stevick and Kahn [245] to go beyond these two objectives and, in addition to direct contacts, obtain from the patient the names of persons he or she may have reason to think may be infected for reasons other than direct contact with the patient. The fundamental defects inherent in this pernicious practice were promptly apparent, and, although fairly effective as a case-finding procedure, it was soon discontinued.

Prevalence of Syphilis.

The unique studies on syphilis in the Eastern Health District of Baltimore by Johns Hopkins University [246] have been further expanded

244. Denison, G. A., and Smith, W. H. Y.: Mass Venereal Disease Control in Urban Area, South. M. J. **39**:195 (March) 1946. Smith, W. H. Y., and Denison, G. A.: Blood Testing and Treatment Program in Jefferson County, Alabama, J. Ven. Dis. Inform. **27**:94 (April) 1946.

245. Hazlehurst, W. D.; Stevick, C. P., and Kahn, H. A.: Preliminary Report Evaluating the Worth of Obtaining Names of Suspected Contacts During a Regular Contact Interview, J. Ven. Dis. Inform. **27**:65 (March) 1946.

246. (a) Turner, T. B.: Studies on Syphilis in the Eastern Health District of Baltimore City: I. Principles Concerned in Measuring the Frequency of the Disease, Am. J. Hyg. **37**:259, 1943. (b) Turner, T. B.; Dyar, R.; Clark, E. G., and Birkhead, M. F.: Studies on Syphilis in the Eastern Health District of

by Clark,[247] who has determined the accumulated prevalence of syphilitic infection in this carefully enumerated population group, studying the influence of such factors as race, sex, age and socioeconomic status. These long range studies are based on two basic sources of data: records of population enumeration of residents of the Eastern Health District and records pertaining to the status of syphilis contained in an accumulative file on cases of syphilis and serologic status of patients. In general, the data make possible accurate quantitative determinations of the prevalence of syphilis in this locality, which eventually can be applied to accurate determinations of the trend of syphilis.

In the present article, the prevalence of known syphilis among white men was determined as 0.85 per cent and that of known syphilis plus history of treatment was 0.95 per cent of the population. Among white women, the prevalence of known syphilis was 0.70 per cent and that of known syphilis plus history of treatment 0.91 per cent. The highest rate among white men was in the 50 to 59 year age group and among white women in the 35 to 39 year group. Among Negro men the prevalence of known syphilis was 12.9 per cent; known syphilis plus history of treatment, 15.5 per cent, and estimated (on the basis of an additional and previously demonstrated to be pertinent factor), 19.5 per cent. Among Negro women, the prevalence of known syphilis, 16.2 per cent; known syphilis plus history of treatment, 19.3 per cent, and estimated, 21.0 per cent. In both Negro sexes, syphilis was most prevalent in the 35 to 39 year group.

Higher rates were found among divorced and separated persons than among those married or single. Figures for prevalence among persons classified according to the usual occupation of the head of the household showed little variation among white persons, although highest among the servant class. Among Negroes, on the other hand, the professional and proprietor class had a significantly lower rate than any of the other classes. This rate was 8.8 per cent, eight times higher than that of the

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Baltimore City: II. Discovery Rates as an Index of Trend, ibid. **37**:273, 1943. (*c*) Clark, E. G., and Turner, T. B.: Studies on Syphilis in the Eastern Health District of Baltimore City: III. Study of the Prevalence of Syphilis Based on Specific Age Groups of an Enumerated Population, Am. J. Pub. Health **32**:307, 1942. (*d*) Clark, E. G.; Turner, T. B.; Leiby, G. M., and Dyar, R.: Studies on Syphilis in the Eastern Health District of Baltimore City: IV. The Prevalence of Syphilis Among Parturient Women as an Index of the Trend of Syphilis in the Community, to be published. (*e*) Clark, E. G.; Cross, M. C., and Mason, J. S.: Studies on Syphilis in the Eastern Health District of Baltimore City: V. An Analysis of Serologic Tests Done from 1937-1939, to be published.

247. Clark, E. G.: Studies on Syphilis in the Eastern Health District of Baltimore City: VI. Prevalence in 1939, by Race, Sex, Age, and Socioeconomic Status, Am. J. Syph., Gonor. & Ven. Dis. **29**:455 (July) 1945.

white servant class. In general, the rates varied directly with educational attainment among both Negroes and white persons, the lowest rate being among persons with college education.

Economic Cost.

The suffering of the individual patient with dementia paralytica cannot be expressed in terms of dollars and cents, but the economic costs of this condition to the community can be approximated. According to Iskrant,[248] it costs the United States taxpayer at least $11,000,000 a year to maintain the paretic population of the nation. In addition, the annual loss of productive capacity (of paretic men only) approximates $112,000,000 a year. Further and incalculable expenses incurred by the community are the burden imposed on public and private charity for caring for paretic persons and their dependents, the cost of crimes committed by paretic persons and by the juvenile delinquency of their neglected children and financial losses caused by the wild speculation (sometimes with public funds) of some patients with early paralysis.

Historical Aspects of Syphilis.

At various times the destinies of mankind have been, as Podolsky[249] records, in the hands of rulers with syphilis of the central nervous system, and the disease significantly has altered the course of world history. This writer states the belief that the Tudors of England, Ivan the Terrible of Russia, Frederick the Great of Prussia, Louis IV of France and Mussolini, the Duce of Italy, all were conditioned in their actions by syphilitic involvement of the brain. How significantly these rulers influenced the expansion and national development or the political downfall of their respective countries is discussed.

Of the many theories of the origin of syphilis proposed by early observers, one of the most curious is to be found in the writings of an Englishman, George Sandys. The author, who was the seventh son of Edwin Sandys, Archbishop of York, was born in 1578. A great traveler, he visited many parts of Europe and the Near East and took part in the colonial development of Virginia. Although not a physician, he appears to have paid great attention to matters of medical interest encountered in his travels.

The following passage from Sandys' book, quoted by Riddell,[250] indicates the early belief that cannabalism was a factor in the early spread of syphilis throughout the Old World:

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248. Iskrant, A. P.: The Economic Cost of Paresis in the United States, J. Ven. Dis. Inform. **26**:175 (Aug.) 1945.

249. Podolsky, E.: The Syphilitic Brain and Human Destinies, M. Rec. **159**: 40 (Jan.) 1946.

250. Riddell, W. R.: An Old Theory of the Origin of Syphilis, Urol. & Cutan. Rev. **50**:144 (March) 1946.

I have read or heard how certaine merchants being bound to serve the *French* army at the siege of *Naples* with so many tun of Tunny, and not able to performe it; hearing of a late fought battell in *Barbarie*, repaired to the place, and supplied the quantitie of mans flesh drest in the same manner: which proued so over-high a feeding . . . that their bodies brake forth into lothsome vlcers; and from that infection the disease that taketh from them the name [Morbus Gallicus], not knowne before in our parts of the world, was introduced amongst us. And *Scaliger* . . . doth also affirme that it proceeded not originally from the impuritie of women, but from contaction; and that the *Spaniards* did first transport these rare wares from the *Indians*, as common amongst them as the measels amongst vs, and equally contagious. Which seemeth to confirme the former assertion, they hauing bene man-eaters for the most part.

SYPHILIS AND OTHER DISEASES

Yaws.—To what extent the immunity conferred by yaws protects against syphilis and vice versa is a question of considerable interest, which has not been fully elucidated by investigations with animals.

An experiment in which a patient with tertiary yaws (who received a total of 3.6 Gm. of neoarsphenamine but who remained seroresistant) was inoculated with T. pallidum from a patient with primary syphilis is reported by Findlay and Willcox.[251] After an incubation period of twenty-one days, a dark field positive chancre with a satellite bubo appeared. It thus would seem that this patient with persistent serologic evidence of yaws was capable of infection with the organism of syphilis.

A preliminary report on the penicillin treatment of 499 patients with primary and secondary yaws infections in Haiti has been made by Dwinelle and his Army associates.[252] Three schedules of therapy were used: Two hundred patients were hospitalized and given a total of 1,200,000 units of penicillin sodium over a period of four days. One hundred and fifty patients were treated on a two day ambulatory basis with penicillin calcium in beeswax and peanut oil. One hundred and forty-nine ambulatory patients received penicillin-beeswax-peanut oil in divided doses over a period of one day.

The clinical response was excellent. Primary and secondary lesions showed evidence of healing within twenty-four hours; pains in the joints disappeared in twenty-four to forty-eight hours, and plantar and palmar "crab" lesions became painless in forty-eight to seventy-two hours. The serologic response was less striking and somewhat less satisfactory than ordinarily occurs in penicillin-treated early syphilis. Whereas one would expect serologic reversal of 70 to 80 per cent of

251. Findlay, G. M., and Willcox, R. R.: A Human Experiment on the Relationship of Yaws and Syphilis, Brit. M. Bull. **3**:197, 1945.

252. Dwinelle, J. H.; Rein, C. R.; Sternberg, T. H., and Sheldon, A. J.: Preliminary Report on the Evaluation of Penicillin in the Treatment of Yaws, Am. J. Trop. Med. **26**:311 (May) 1946.

patients treated within six months in a group of patients with early syphilis who had received a similar amount of penicillin therapy, in only 10 per cent of these patients with early yaws was seronegativity attained.

The immediate clinical and serologic results obtained with penicillin-oil-beeswax appeared to be as good as those with the aqueous solutions. The authors point out that the development of a successful one day treatment schedule is of great practical value in countries such as Haiti, where large numbers of patients must be treated on an ambulatory basis in rural clinics.

Cancer of the Penis.—Because cancerous and precancerous lesions of the penis not infrequently enter into the differential diagnosis of syphilis, the review by Melicow and Gunem [253] is of interest. The prognosis of carcinoma of the penis is so poor and early diagnosis and radical operation so urgent that syphilotherapeutists would do well to follow these authors' advice to use caution in instituting antisyphilitic therapy in patients with atypical penile lesions. The delay incident to a therapeutic test may allow time for inoperable metastases. The differential diagnosis of carcinoma, leukoplakia, erythroplasia, Paget's disease and Bowen's disease is discussed.

253. Melicow, M. M., and Gunem, E. J.: Cancerous and Precancerous Lesions of the Penis: A Clinical and Pathological Study Based on Twenty-Three Cases, J. Urol. **55**:486 (May) 1946.

REVIEW OF NEUROPSYCHIATRY FOR 1946

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IN RECENT years a great deal of work has been done on the psychologic aspects of mental disorder. The literature which has accumulated is enormous. Many writers have ignored the obvious fact that etiology is a complex question, that causes are multiple, and have said loosely that mental illness is psychologic or emotional in origin. A smaller, but persistent voice has also been raised, saying that much could be learned through biologic chemistry. Not much has been done about it but gradually good work in this field is accumulating. Folch [1] read a paper at the opening of a new research laboratory at the McLean Hospital in May 1946. He reviewed the contributions chemistry had made to psychiatry and outlined plans for the future. He explained that the brain has certain unique features: (1) lack of a lymphathic system, (2) abundant blood supply, with poor vasomotor control, (3) high consumption of oxygen, (4) specialized metabolism, (5) chemical composition different from other organs and (6) a mechanism separating the brain from the rest of the body, i. e., the blood-brain barrier. There is important recent work on several of these problems.

CEREBRAL BLOOD FLOW AND CONSUMPTION OF OXYGEN

The brain has a relatively great consumption of oxygen; in man it is second only to the thyroid in this respect. When the body is at rest the brain utilizes approximately one quarter of all oxygen consumed, [2] and about one fifth of the cardiac output goes to the brain. The arterio-venous difference in oxygen content is greater in the brain than in other organs. The brain not only can use oxygen at a high tension but it can extract oxygen from the blood when it is low in oxygen; for example, from venous blood. Under normal conditions the brain extracts about 40 per cent of the oxygen carried to it by the blood. When, therefore,

1. Folch, J.: Biochemical Problems Related to Psychiatry, in Psychiatric Research, Harvard University Monographs in Medicine and Public Health, no. 9, Cambridge, Mass., Harvard University Press, 1947.

2. Kety, S. S., and Schmidt, C. F.: Effects of Active and Passive Hyper-Ventilation on Cerebral Blood Flow, Cerebral Oxygen Consumption, Cardiac Output and Blood Pressure of Normal Young Men, J. Clin. Investigation 25:107, 1946.

the blood is low in oxygen, there is not enough for the brain, a state of affairs which rapidly results in impairment of cerebral function with such symptoms as syncope, stupor and convulsions. Further deprivation of oxygen causes irreversible lesions in the brain and eventually death.

Morrison[3] studied the brains of dogs and monkeys exposed to various degrees of anoxia. Not only was the effect of exposures to extreme degrees of anoxia studied, but the effect of repeated exposures to milder degrees of anoxia, not usually considered detrimental. For example, 1 dog was given thirty-three exposures of three hours each to atmospheres which caused the oxygen content of his blood to fall to 12 volumes per cent. He showed slight lesions in the gray matter. Another dog with 12 exposures at 9 volumes per cent showed pronounced lesions in both gray and white matter. With repeated exposures to mild hypoxia, it was observed that the first histologic changes occurred in the cell bodies of the cortical gray matter. This took place at a level of about .12 or 13 volumes per cent of oxygen in the blood if the exposures were long enough and were repeated often enough. When the percentage of oxygen was reduced still lower, to about 10 volumes per cent, and the number of exposures was increased, the white matter also became involved and presented a pattern of demyelination in the corpus callosum and in the white matter of the cerebral hemispheres. The lesions in their distribution and demyelination had a resemblance to those of Schilder's disease.

Nitrous oxide anesthesia is an alarming hazard at the present time, since want of oxygen is advocated deliberately to aid anesthesia. The available evidence indicates that nitrous oxide should never be administered with a concentration of oxygen below 20 per cent. The current use of anoxia as an adjunct to nitrous oxide–oxygen anesthesia has been the cause of death from asphyxia, psychoses from permanent damage of the brain, and defects of personality which may or may not be recognized.[4]

Schmidt[5] has shown that when the consumption of oxygen by the brain falls below half its normal amount, due to lack of oxygen supply through the blood, the lesions appear and are not reversible. This may occur in anoxia, shock or hemorrhage. In Schmidt's animals picrotoxin increased the consumption of oxygen by the brain to twice the normal amount if enough of the drug were used to cause convulsions. On the

3. Morrison, L. R.: Histopathologic Effect of Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **55**:1 (Jan.) 1946.

4. Barach, A. L., and Rovenstine, E. A.: Hazard of Anoxia During Nitrous Oxide Anesthesia, Anesthesiology **6**:449, 1945.

5. Schmidt, C. F.; Kety, S. S., and Pennes, H. H.: Gaseous Metabolism of the Monkey Brain, Am. J. Physiol. **143**:33, 1945.

other hand, experimentally produced thyroid disturbances do not change the utilization of oxygen by the brain.[6]

Knowledge about the respiration of the central nervous system has been well reviewed by Quastel.[7] He measured the metabolic rate of the brain by working on samples of excised tissue. Since then the metabolism of the brain has been estimated in vivo in laboratory animals and in man. Kety and Schmidt [8] recently developed a method of determining cerebral flow of blood in man. The subject inhaled a mixture of 15 per cent nitrous oxide, 21 per cent oxygen and 64 per cent nitrogen, with a mixture of calcium oxide and sodium hydroxide (soda lime) to remove the carbon dioxide from the closed system. Simultaneous samples of blood were drawn from an internal jugular vein and a femoral artery at approximately one, four, seven and ten minutes after the beginning of the inhalation of the gas. The samples of blood were analyzed for nitrous oxide, oxygen and carbon dioxide. From the values of nitrous oxide the cerebral blood flow can be calculated, and from the other values the difference in the oxygen content of the cerebral arteries and the cerebral veins can be determined. With these data in hand the metabolic rate can be figured in terms of consumption of oxygen per hundred grams of cerebral tissue per minute. The metabolic rate is found to be about 3.7.

Gibbs, Maxwell and Gibbs [9] have measured cerebral blood flow by injecting a dye into an artery supplying the brain and determining its concentration in the returning venous stream. They did this in several human cases and checked it against a direct volumetric measurement of blood flow in 1 case. They found that the average flow is 617 millimeters per minute and computed the average consumption of oxygen as 39.2 millimeters per minute. Figured as cubic centimeters per hundred grams of brain tissue per minute, this gives a result of about 3 for a metabolic rate. This is considerably lower than the figure of Kety and Schmidt, but at least it is within the same range, and the differences will have to be explained when the technics have been used on larger numbers of subjects. At least there are now available an approximation of what the human cerebral blood flow is and a fairly accurate determination of cerebral metabolism. Gibbs found that hyper-

6. Fazekas, J. F.: Cerebral Metabolism of Hyperthyroid, Thyroid Deficit and Cretinous Rats, Federation Proc. 5:26, 1946.

7. Quastel, J. H.: Respiration in Central Nervous System, Physiol. Rev. 19:135, 1939.

8. Kety, S. S., and Schmidt, C. F.: Determination of Cerebral Blood Flow in Man by the Use of Nitrous Oxide in Low Concentration, Am. J. Physiol. 143:53, 1945; footnote 2.

9. Gibbs, F. A.; Maxwell, H. P., and Gibbs, E. L.: Volume Flow of Blood Through the Brain of Man at Rest, During Hyperventilation and While Breathing High CO_2, Federation Proc. 5:33, 1946.

ventilation greatly reduced blood flow and that inhalation of carbon dioxide increased it.

Himwich and his colleagues [10] used the methods of Kety and Schmidt to study the metabolism of the brain during pentothal anesthesia. In normal controls Himwich found the metabolic rate to be about 3.3 cc. of oxygen per hundred grams per minute. This is about halfway between Gibbs's figures and those of Kety and Schmidt. With the subject under pentothal anesthesia the values fell to 2.1 cc. during the third stage of anesthesia. Obviously cortical excitation is depressed, and this is probably the main cause of narcosis, but comparison with patients suffering from metabolic depression in hypoglycemia coma [11] suggests that pentothal also directly depresses nerve function.

All of these observations both on animals and man deal with the oxygen consumption of the brain, considered as a single organ. They do not take into account the fact that the vascular structure of any given region of the brain is in proportion to its metabolic demands. Evidence for this is put forward by York, Homburger and Himwich [12] from the physiologic side. It has long been known that gray matter and certain nuclei in the brain had a much richer capillary network than white matter.[13] The idea that the observed quantitative differences in the capillary bed are related to metabolic activity is based on good evidence. In some areas in which nerve cells were not abundant but capillaries were, the discrepancy has been explained by the great number of synaptic structures in these areas even though nerve cells were present in only moderate numbers.

Mitochondria are found to be abundant where the nerve cells and their dendrites (neuropil) are highly vascular. Scharrer [14] has studied this by combining injection of the capillaries with especial stains for mitochondria. The correlation between density of capillaries and abundance of mitochondria appears to be the expression of a functional relationship. This fits in with Campbell's [15] observation that oxidase

10. Himwich, H. E.; Homburger, E.; Maresca, R., and· Himwich, W. A.: Brain Metabolism in Man: Unanesthetized and in Pentothal Narcosis, Am. J. Psychiat., to be published.

11. Himwich, H. E., and others: Cerebral Blood Flow and Brain Metabolism During Insulin Hypoglycemia, Am. J. Physiol. **132**:640, 1941.

12. York, G. E.; Homburger, E., and Himwich, H. E.: Similarity of Cerebral Arteriovenous Oxygen Differences on Right and Left Sides in Resting Man, Arch. Neurol. & Psychiat. **55**:578 (June) 1946.

13. Craigie, E. H.: Architecture of the Cerebral Capillary Bed, Biol. Rev., London **20**:133, 1945.

14. Scharrer, E.: Capillaries and Mitochondria in Neuropil, J. Comp. Neurol. **83**:237, 1945.

15. Campbell, A. C. P.: Variation in Vascularity and Oxidase Content in Different Regions of the Brain of the Cat, Arch. Neurol. & Psychiat. **41**:223 (Feb.) 1939.

content in the brain is high where capillaries are densely clustered. Since mitochondria are carriers of respiratory enzymes the observations are all the more significant. Moreover, the brain has variations in blood flow which correspond to the active and quiescent areas. For example, there is increased flow in the occipital areas when the eyes are being used and in the olfactory bulb when a strong smell is being inhaled. This has been shown by a number of investigators.[16] Before the oxygen consumption of the brain is really well understood, there must be more studies of this local action. At present there is only proof that such action occurs in the occipital and parietal areas of the cortex, in the olfactory bulb and in the medulla.

McCulloch [17] and his co-workers have studied localized areas in the cortex of living animals for changes in p_H, lactic acid content and oxygen tension. The method of determining oxygen tension by electrical means in vivo was first employed by Bronk in the Johnson Foundation Laboratory at the University of Pennsylvania. McCulloch, at Illinois, has modified the method and applied it to the cortex of the cat, to see what changes occurred when the animal breathed nitrogen, when the cerebral blood flow was increased and when flow was reduced. Inhalation of nitrogen produced a precipitous fall in cortical oxygen tension. Decreasing blood flow caused a fall and increased blood flow a rise in oxygen tension. Breathing oxygen instead of air increases the tension in the cortex by 75 per cent, but this does not seem to affect the oxygen consumption of the cortex because the electrical activity of the cortex is not affected.

It has long been known that the energy of the brain is the result of a special type of metabolism; i. e., the brain derives its energy entirely from the combustion of dextrose, while most tissues burn either carbohydrates or ketones. The brain does not need insulin for the utilization of the pituitary diabetogenic hormone.[18] The work of Caspersson [19]

16. Schmidt, C. F., and Hendrix, J. P.: Action of Chemical Substances on Cerebral Blood-Vessels, A. Research Nerv. & Ment. Dis., Proc. (1937) **18:**229, 1938. Gerard, R. W.: Brain Metabolism and Circulation, ibid. **18:**316, 1938. Cobb, S., and Talbott, J. H.: Studies in Cerebral Circulation: Quantitative Study of Cerebral Capillaries, Tr. A. Am. Physicians **42:**255, 1927.

17. Roseman, E.; Goodwin, C. W., and McCulloch, W. S.: Rapid Changes in Cerebral Oxygen Tension Induced by Altering the Oxygenation and Circulation of the Blood, J. Neurophysiol. **9:**33, 1946.

18. Price, W. H.; Cori, C. F., and Colowick, S. P.: Effect of Anterior Pituitary Extract and of Insulin on the Hexokinase Reaction, J. Biol. Chem. **160:**633, 1945.

19. Caspersson, T.: Studies on Protein Metabolism in the Cells of Epithelial Tumors, Stockholm, P. A. Norstedt & Söner, 1942; On the Role of the Nucleic Acids in the Cell, in Proceedings of the Seventh International Genetical Congress, 1939, London, Cambridge University Press, 1941, p. 85.

has shown that there are various other metabolic activities in the brain, such as changes in the nucleoproteids when the nerve cells become active. These metabolic changes, however, are small and require extremely small amounts of energy, so that in general the statement may be made that the brain derives its energy from dextrose. The changes in the nucleo-proteids described by Caspersson are, nevertheless, of great interest and show that changes take place in the active nerve cell rapidly and are reversible with cessation of this activity. They show that the proteids act differently within the nucleus and outside of it. Obviously more experiments are needed to study these chemical changes, and new meth-ods are being developed which bring out the microchemical activities of the neurons.

THE BARRIER

Among the unique characteristics of the brain mentioned by Folch was the blood-brain barrier. This has been known to exist for a long time, because certain stains and toxins were observed which did not enter the brain from the blood. There must be, in fact, not only a blood-brain barrier, but a blood–spinal fluid barrier, which would lie in the choroid plexus, and a spinal fluid–brain barrier, which would be the pia and the lining of the perivascular spaces. Thus from the histologic point of view there is a barrier which must come down to something similar in structure to a capillary wall. Such a wall, however, is not sufficient to explain the action as a barrier, and one has to resort to chemistry. By using isotopic tracers it has been found that such substances as potas-sium, choline, lactic acid and pyruvic acid spread into the brain substance at a much slower rate than they diffuse into other tissues. This is probably due to the positive or negative charges on these ions, as explained by Friedemann.[20] Although much remains to be learned about the actual mechanism, there is no doubt that much of the "barrier" is caused by the chemical and osmotic relationships of the tissues on each side of the wall. Such relationships are probably more important in causing the barrier than the structure of the wall itself.

Kalz, Friedman, Schenker and Fischer[21] by an investigation of "false positive" Wassermann reactions came to the conclusion that reagin passes more easily from the serum to the spinal fluid in infants and in syphilitic patients than in normal controls. It has long been known that in newborn animals many substances pass freely from blood to spinal fluid which later in life are prevented from passing the barrier. Few observations have been made on human subjects. Kalz and his

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20. Friedemann, U.: Blood-Brain Barrier, Physiol. Rev. **22**:125, 1942.

21. Kalz, F.; Friedman, H.; Schenker, A., and Fischer, I.: Permeability of Blood-Spinal Fluid Barrier in Infants and in Normal and Syphilitic Adults, Arch. Neurol. & Psychiat. **56**:55 (July) 1946.

colleagues determined the permeability of the barrier by Walter's bromide method. The bromide content of the blood is divided by the bromide content of the spinal fluid to give the "bromide permeability quotient." In 22 normal infants this was found to be between 1.21 and 3.39, with the mean near 2. In normal adults the range was from 2.1 to 3.9, with the mean at about 3. For adults with active neurosyphilis they found a range from 0.09 to 2.89, with the mean at 2.03. These results indicate that in infancy and in active infection of the central nervous system the permeability of the barrier is so changed that molecules of the size of those of reagin can easily pass through from blood to spinal fluid. In adults with normal meninges and ependyma and vessels such molecules cannot pass. This not only explains the "false-positive" Wassermann reactions but gives an excellent example of the action of the "barrier" in man.

CAUSALGIA

In this war the causalgia syndrome has developed in from 2 to 3 per cent of men suffering from penetrating wounds affecting the nerves of an extremity. The commonest site is the median nerve. The symptoms are well known from the wounded of former wars and occasional civil cases. There is burning pain in the sensory distribution of the injured nerve. This pain is constant and severe; it is made excruciating by touching or even by currents of air. Psychic disturbances bring on exacerbations. The victim becomes a recluse, nursing his limb and keeping away from stimuli. Trophic changes occur in the skin; it becomes shiny and smooth. The subcutaneous tissues and bones may show atrophy. There is considerable sweating and vasomotor change. Little relief has been given by curing local infection, freeing the nerve from adhesions, section of posterior roots and periarterial sympathectomy. Recently sympathetic denervation of the arm or leg has been found to be remarkably successful.[22] It appears that elimination of the efferent sympathetic discharge to the painful limb stops the pain. The implications of this surgical result are interesting.

Clinically it can be shown that the burning pain of causalgia occurs in direct relationship to the tonic vasomotor, sudomotor and pilomotor discharge over the sympathetic efferent pathways.[23] Cold or excessive heat, loud noises, jars, any excitement or emotional tension and hypodermic injections in any part of the body set up burning and sweating in the affected area. Indeed those factors that usually set up sympathetic discharge cause pain. On the other hand, blocking the sympathetic

22. White, J. C.: Painful Injuries of Nerves and Their Surgical Treatment, Am. J. Surg. **72**:468, 1946. Rasmussen, T. B., and Freedman, H.: Treatment of Causalgia: Analysis of One Hundred Cases, J. Neurosurg. **3**:165, 1946.

23. White, J. C.: Read before the Harvey Cushing Society, Oct. 13, 1946.

efferent discharge with tetraethyl ammonium bromide [24] or a warm quiet room or sleep causes the pain to stop. Mitchell in his original essay on the subject said: "I have heard men remark that it took some time to get awake to the pain."

The best theory to explain all this is that efferent nervous discharge along sympathetic fibers in a nerve can cause direct cross stimulation of the poorly myelinated afferent pain fibers near the point of injury.[25] Experimental evidence of Katz and Schmitt [26] that efferent nerve impulses can alter the excitability of adjacent afferent axons makes this theory probable. Furthermore, Granit, Leksell and Skoglund [27] have shown that such cross stimulation between motor and sensory neurons does take place. They recorded with a cathode ray oscillograph afferent discharges from the sensory root when the motor root was stimulated after partial injury to the nerve trunk in the periphery.

From the practical standpoint this means that in order to cure the pain of causalgia either the environment must be so restricted that no sympathetic discharge occurs in the patient's nervous system or sympathetic pathways to the affected limb must be interrupted. The former method led to chronic invalidism and frequently to suicide. The surgical operation of sympathectomy for a limb has now been so well perfected that the cure of this postwar torture for many wounded men is practically assured.

DERMATOMES AND RESISTANCE OF THE SKIN

The distribution of the sympathetic nerves to the skin was not well understood until Richter [28] published his important researches on the resistance of the skin of monkeys with experimental nerve block and on man in cases of injury of peripheral nerves and sympathectomy. The main facts are as follows:

(1) The resistance offered to the passage of a minute, imperceptible, direct current through the body is localized almost entirely in the skin. . . .

24. Berry, R. L., and others: Use of Tetraethylammonium in Peripheral Vascular Disease and Causalgic States, Surgery 20:525, 1946.

25. Doupe, J.; Cullen, C. H., and Chance, G. Q.: Post-Traumatic Pain and Causalgic Syndrome, J. Neurol., Neurosurg. & Psychiat. 7:33, 1944.

26. Katz, B., and Schmitt, O. H.: Electric Interaction Between Two Adjacent Nerve Fibres, J. Physiol. 97:471, 1940.

27. Granit, R.; Leksell, L., and Skoglund, C. R.: Fibre Interaction in Injured or Compressed Region of Nerve, Brain 67:125, 1944.

28. Richter, C. P.: Instructions for Using the Cutaneous Resistance Recorder, or Dermometer, on Peripheral Nerve Injuries, Sympathectomies, and Paravertebral Blocks, J. Neurosurg. 3:181, 1946. Bruesch, S. R., and Richter, C. P.: Cutaneous Distribution of Peripheral Nerves in Rhesus Monkeys as Determined by the Electrical Skin Resistance Method, Bull. Johns Hopkins Hosp. 78:235, 1946. Richter, C. P., and Woodruff, B. G.: Lumbar Sympathetic Dermatomes in Man Determined by the Electrical Skin Resistance Method, J. Neurophysiol. 8:323, 1945.

(2) Skin resistance is controlled largely through the nervous system. Thus, section of a peripheral nerve trunk produces a great and permanent increase in the resistance of the skin supplied by that nerve, while stimulation or irritation of the nerve has the opposite effect, producing a decrease in the skin resistance.

(3) Skin resistance depends on the sympathetic component of the peripheral nerves. Thus, it has been shown that: (a) Elimination of the sympathetic supply by ganglionectomy, while leaving the motor and sensory fibers intact, produces an increase in skin resistance as great as that produced by section of the entire nerve trunk. . . . (c) Factors stimulating the sympathetic nervous system, such as external heat, muscular effort, emotional excitement, or mental tension, tend to decrease skin resistance. The opposite is true of factors decreasing sympathetic activity, such as rest, sleep, relaxation, and freedom from mental tension. These act to increase skin resistance.

(4) Skin resistance varies directly with sweat gland activity, becoming low when the sweat glands are active and high when they are inactive.

The practical application of this knowledge is by means of an instrument devised by Richter and called a dermometer. Jasper [29] has modified this instrument and calls it a "dermohmmeter." This not only maps out accurately the areas where sympathectomy has deprived the skin of sympathetic innervation, but incidentally is a most accurate and objective way of checking on the areas of anesthesia caused by lesions of peripheral nerves. Ordinary clinical methods depend on the answers of the patient in response to stimuli. The "dermometer" gives a simple, objective method that can be applied to a child, a monkey, a malingerer or a patient in coma.

At the St. Albans Naval Hospital and the New York Neurological Institute cooperative research was carried out by Herz, Glaser, Moldaver and Hoen,[30] who studied a larger group of injuries of peripheral nerves, 87 cases of injury of individual nerves and 15 of injury of plexuses. They found that where there was complete sensory loss the area where the resistance of the skin was elevated corresponded almost exactly in 47 out of 51 cases. This demonstrates the value of the "dermohmmeter" in mapping out anesthetic areas. The results of mapping out areas of hypesthesia were less satisfactory. In only 13 out of 40 cases was there good correlation between the areas of partial sensory loss and heightened cutaneous resistance. In 16 cases there was no change in the resistance of the skin. It may be that in these cases the sympathetic nerves regenerated before the sensory nerves. This is a plausible explanation because the regenerative powers of the autonomic system are known to be great.

29. Jasper, H. H.: Improved Clinical Dermohmmeter, J. Neurosurg. **2**:257, 1945.

30. Herz, E.; Glaser, G. H.; Moldaver, J., and Hoen, T. I.: Electrical Skin Resistance Test in Evaluation of Peripheral Nerve Injuries, Arch. Neurol. & Psychiat. **56**:365 (Oct.) 1946.

ELECTRIC SHOCK THERAPY

Practically all psychiatrists now agree that electric shock is of value in the affective psychoses.[31] It is probably most beneficial in the involutional depressions, over 80 per cent being conspicuously improved. This is important in a condition in which without treatment protracted depression was the rule, sometimes lasting for years. In manic-depressive patients, especially in the depressed phase, there is also about 80 per cent recovery after electric shock, but it must be remembered that the attacks of this disease are self limited and that if the patients were left untreated 80 to 90 per cent would recover spontaneously. The risk of suicide, however, is great, and shock treatment will save a certain number of patients who would kill themselves if left alone.[32] Moreover, the shock treatment shortens the depressions and saves the patient many weeks or months of unhappiness. In schizophrenia electric shock is largely of use as a symptomatic treatment to quiet disturbed patients. Many schizophrenic patients have appeared to improve after courses of electric shock, but most of them later relapse.

The long courses of treatment, fifty or more shocks, producing profound organic sensorial defects equivalent to an amentia[33] seem hardly justifiable. Many patients seem to be able to stand repeated shocks but others show pronounced deterioration after long courses. Brody[34] reported 6 cases of prolonged impairment of memory leading to disability. A brief loss of memory occurs after each shock, and a defect may be present for days or weeks after a course of eight or ten treatments. It is only after repeated courses of treatment that the loss seems to be prolonged or permanent. On the other hand, patients have failed to show deterioration after as many as 248 electroconvulsive shocks.[35]

Such conflicting observations make one wonder just what goes on in the brain when electric currents strong enough to cause convulsions are passed through the frontal lobes. Many experimental studies have been made. In the laboratories of ten different experimenters animals have been given convulsive shocks and the brains afterward examined. Five reported cerebral lesions and five said that there were no lesions

31. Solomon, H.: Shock Therapies in Psychiatry, Clinics **4**:555, 1945.

32. Ziskind, E.; Somerfeld-Ziskind, E., and Ziskind, L.: Metrazol and Electric Convulsive Therapy of the Affective Psychoses: A Controlled Series of Observations Covering a Period of Five Years, Arch. Neurol. & Psychiat. **53**:212 (March) 1945.

33. Bennett, A. E.: Evaluation of Electric Shock Therapies, Psychiatric Quart. **19**:465, 1945.

34. Brody, M. B.: Prolonged Memory Defects Following Electro-Therapy, J. Ment. Sc. **90**:777, 1944.

35. Perlson, J.: Psychologic Studies on a Patient Who Received Two Hundred and Forty-Eight Shock Treatments, Arch. Neurol. & Psychiat. **54**:409 (Dec.) 1945.

or that the lesions were not significant. Most of the experiments did not closely enough duplicate the conditions pertaining in human electro-shock therapy to be important in answering the question. The most recent paper is the most convincing. Ferraro, Roizin and Helfand [36] used monkeys, observed them for months and used currents comparable to those used in therapy, taking into account the smaller size of the monkey brain. The 10 monkeys reported on in this paper received from four to eighteen convulsive shocks, an average number of ten each. All showed histologic changes in the brain. These were mostly in the frontal lobes, the part of the brain through which the current was passed. The commonest changes were in the nerve cells, which showed pyknosis, swelling and other changes. There were also swelling and proliferation of the glia. Capillary hemorrhages were common. The severity of the changes seemed to bear a relation to the intensity and duration of the current and to the number of electric shocks given. The authors believe that the changes in the nerve cells "are mostly the reversible type." This, however, is a matter of opinion. From the photographs in the paper one might consider some of the changes rather severe and likely to lead to cell death. It is probable, however, that man has a great many more nerve cells in his brain than he ever uses, so that many may be destroyed without causing permanent mental symptoms. In other words, there is a good margin of safety. Just how wide this margin actually is nobody at present can say.

A good review of the English experience with shock is given by Pullar-Strecker,[37] who sums up the situation well by saying:

In Great Britain alone, E. C. T. [electrical convulsion therapy] has been applied to . . . about 10,000 patients of all ages up to 75. Six deaths were reported up to June 1944. [Complications occurring during or after treatment include:] (1) Dislocation of jaw and shoulder, fracture of humerus and femur, compression fracture of vertebra. . . . (2) Brain damage, such as impairment of the memory or intellectual deterioration. The latter is extremely rare, the former quite frequent, temporarily. . . . (3) Activation of old quiescent tuberculosis, . . . responsible for most of the deaths reported. (4) Undesirable mental sequelae, such as excitement, confusion, violence; aggravation of existing symptoms. . . . (5) Cardiovascular accidents. [These] no longer occur with reasonable selection of patients. (6) Activation of latent epilepsy.

. . . Absolute contra indications are recent tuberculosis, intracranial disorders, organic diseases of the central nervous system, and, temporarily, the presence of infection. . . .

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36. Ferraro, A.; Roizin, L., and Helfand, M.: Morphologic Changes in the Brain of Monkeys Following Convulsions Electrically Induced, J. Neuropath. & Exper. Neurol. **5**:285, 1946.

37. Pullar-Strecker, H.: Scope of Electrical Convulsion Therapy, M. Press **214**:192, 1945.

[More often than not, electrical convulsion therapy reclaims the depressive.] The time factor, i.e., the duration of the illness, does not adversely affect results. . . . No more than 15 per cent of depressive patients remain unimproved by this treatment.

Other shock therapies are still being used. Metrazol convulsions, because of the fear reactions in the patients, are being used less and less. Insulin still holds an important place in the treatment of schizophrenia. In Russia [38] hemocolloidoclastic shock is being used successfully. Five or 10 cc. of incompatible blood is injected into a schizophrenic patient. There is immediately an acute disturbance of the vasomotor and vegetative functions with temperature as high as 40 C. (104 F.). In Khalurian's cases improvement occurred in 22 out of 35 cases. Galenko and Kirilova gave as much as 35 cc. of incompatible blood twice a week for a total of eight or ten injections. Among 22 cases of schizophrenia of short duration, considerable improvement occurred in 6 and some improvement in 9 more.

It is often stated that nothing is known of the mechanism by which shock therapy improves patients with psychotic symptoms. The microscopic observations on the pathologic changes in nerve cells certainly give one some conception of what is going on. Gellhorn's [39] physiologic experiments go further and indicate that the important factor may be the increased excitability of the sympathetic nervous system. Especially interesting are his experiments on rats which show that insulin coma and electrical convulsions can lead to a restoration of inhibited conditioned reactions. In discussing the hyperactivity of the sympathetic system he says:

Such effects may persist for considerable periods. It must therefore be assumed that discharges from these centers, particularly from the hypothalamus, are increased above the normal value. Murphy and Gellhorn showed recently that the sympathetic parts of the hypothalamus give rise to impulses afferent to the motor cortex, the primary sensory projection area and the association centers of the brain. These impulses increase the effectiveness of subthreshold stimulation of the motor cortex to such a degree that distinct movements may result. Furthermore, studies of the action potentials of the cortex have shown that under the influence of these hypothalamic impulses the cortical excitability is greatly increased and the number of active neurons enlarged. These data suggest that cortical residues of previously established conditioned reactions may be activated as a result of the heightened hypothalamic activity following insulin coma. This may account for the restoration of inhibited conditioned reactions.

38. Khalurian, G. M.: Nevropat. i psikhiat. **14**:40, 1945. Galenko, V. E., and Kirilova, A. Z.: ibid. **14**:38, 1945.

39. Gellhorn, E.: Is Restoration of Inhibited Conditioned Reactions by Insulin Coma Specific for Pavlovian Inhibitions? Contribution to the Theory of Shock Treatment, Arch. Neurol. & Psychiat. **56**:216 (Aug.) 1946.

LESSONS FROM MILITARY PSYCHIATRY

General Menninger [40] has written an important paper, giving his opinion as to what important lessons were learned from the Army experience concerning psychiatry. His paper will be read by most psychiatrists, who know what a splendid job he did as chief of psychiatry in The Surgeon General's Office. The paper should be read by the dean of every medical school and by every professor of medicine. The war experience dispels once and for all the misconception that psychiatric disorders are "incurable" or do not respond well to treatment. With few and often briefly trained psychiatrists to treat the men with neurosis, 90 per cent were returned to duty overseas and of the 10 per cent sent back to this country between 25 and 50 per cent were salvaged. Even among those with psychotic reactions 70 per cent were able to return to their homes rather than to veterans' hospitals. If it is true that 50 per cent of all patients of all physicians in civil practice have symptoms on a neurotic basis, these figures indicate that a tremendous number of persons have a hopeful prognosis if treatment can be started early. But there's the rub. In the Army the patients were young men; they were under supervision and were sent to a physician as soon as symptoms appeared. In civil life it is exceptional for a patient to seek a psychiatrist in the early stages of his maladjustment. "The lesson would seem to be that psychiatry must aim first towards active, early treatment."

The person in war is exposed to fear, isolation, discomfort, privation and many other new difficulties which tend to disintegrate him. Factors which aided integration were found to be effective leadership, identification with a group, confidence gained from training and conviction as to the importance of the job. Seeing these factors at work on the morale of different groups of men emphasized to psychiatrists and all others who were observant that stress from social forces was a major factor in the causation of psychiatric casualties. This is not new, but it is the sort of thing which is uncritically taken for granted. Here are data.

Another important contribution toward the practical handling of neurotic patients was the way in which auxiliary personnel could be used. Clinical psychologists and psychiatric social workers can help a great deal in diagnosis and treatment. This of course must be supervised by the psychiatrist, and ideally the psychologic interviews should be in the hands of a psychiatrist, but in the face of the shortage of physicians who are interested in or trained in psychiatry it is only practical to make use of these nonmedical assistants. Many more psychiatrically

40. Menninger, W. C.: Lessons from Military Psychiatry for Civilian Psychiatry, Ment. Hyg. **30**:571, 1946.

trained nurses and occupational and educational therapists are also needed.

In treatment the three main contributions, according to Menninger, were:

. . . the improvement of group psychotherapeutic methods, experience with psychotherapy under sedation, and the development of an elaborately organized program of activities for neurotic patients. None of these was essentially new, but each was greatly elaborated and a mass of new experience accumulated.

Group psychotherapy rose to prominence through expediency. It seemed to be the best method for the psychiatrist to spend some additional time with his patients. Following the adage that "necessity is the mother of invention," it became recognized as having many advantages not possible in individual psychotherapy. Most conspicuous of these was the sharing among the group of problems that the individual had assumed to be unique to himself. With the sharing came the finding of solutions in the contributions of other patient failures or successes. The social forces of group opinion, approval or disapproval, became one of group therapy's major advantages that was most effectively developed in the correction installations. This method of treatment seemed to be more effective in changing attitudes than in actually relieving symptoms, but the two can hardly be separated.

Psychotherapy under sedation was widely utilized . . . The experience gained would suggest that it is an extremely valuable short-cut method and that, if properly used and further developed, it might be one of the chief contributions of military psychiatry to civilian practice, as one type of abbreviated psychotherapy.

The third contribution to improved therapeutic technique was possible chiefly because of the almost inexhaustible resources expended by the army for the treatment of disabled soldiers. In the twelve convalescent hospitals of the army service forces and in a considerable number in the air force, an elaborate system was developed. The individual patient with a neurotic reaction was exposed, in consecutive series, to individual psychotherapy, group psychotherapy, and a battery of educational, occupational, and recreational opportunities, hardly available in even the most ideal civilian psychiatric-treatment center in the country.

News and Comment

Wednesday, February 12, 1947

11:00 A. M.   Clinico-Pathological Conference, presented by Sidney Farber, M.D., Department of Pathology, Harvard Medical School, Boston, and Charles D. May, M.D., Associate in Pediatrics, Harvard Medical School, Boston

2:30 P. M.   "Surgical Aspects of Diabetes," Leland S. McKittrick, M.D., Boston

3:30 P. M.   "Recent Advances in the Study and Treatment of Diabetes," Howard F. Root, M.D., Boston

8:00 P. M.   "Viral Hepatitis," Joseph Stokes Jr., M.D., Professor of Pediatrics, University of Pennsylvania Medical School, Philadelphia

9:00 P. M.   "Pericardial Scars," Francis C. Wood, M.D., Assistant Professor of Medicine, University of Pennsylvania Medical School, Philadelphia

Thursday, February 13

11:00 A. M.   Clinico-Pathological Conference, presented by J. E. Ash, Colonel, Medical Corps, Director, Army Institute of Pathology, Washington, D. C., and Wallace Yater, M.D., former Professor of Medicine at Georgetown University

2:30 P. M.   "Some Clinical and Physiologic Aspects of Portal Cirrhosis," Albert M. Snell, M.D., Mayo Clinic, Rochester, Minn.

3:30 P. M.   "The Current Status of Calcium Penicillin in Beeswax and Peanut Oil," Monroe J. Romansky, M.D., George Washington University School of Medicine, Washington, D. C.

8:00 P. M.   "The Present Status of Effective Specific Therapy Based on Exact Hematologic Diagnosis," Charles A. Doan, M.D., Dean, College of Medicine, Ohio State University, Columbus, Ohio

ANNOUNCEMENTS

Research Fellowships in Medicine.—The American College of Physicians offers a limited number of research fellowships designed to provide an opportunity for research training in either the basic medical sciences or the application of the sciences to clinical investigation. The fellowships are for the benefit of physicians who are in the early stages for preparation for a teaching or investigative career in internal medicine, pediatrics and other allied fields. The term of appointment is for one year, usually beginning July 1. The stipend will be from $1,800 to $3,000 per annum. Application forms may be procured from the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa. It is desirable that applications be filed by December 1 each year. Awards will be made on or about January 1.

Postgraduate Courses at the University of California.—The University of California Medical School, with the cooperative administration of University Extension, University of California, will shortly announce a program of postgraduate instruction to be offered at the Medical Center, San Francisco. A variety of courses will be given which will encompass the fields of internal medicine, general surgery, obstetrics and gynecology, otorhinolaryngology, ophthalmology, psychiatry and the basic sciences, as well as a course specially designed to meet the needs of general practitioners here mentioned.

Fees for all these courses will be covered by the provisions of the G. I. Bill of Rights.

A refresher course in internal medicine and general surgery, which will be given February 10 to 14, inclusive, 1947, at the University of California Hospital, Medical Center, San Francisco, is primarily designed for general practitioners. It will include the recent advances in diagnosis and treatment in internal medicine and general surgery. It is open only to graduates of approved medical schools. The fee for this course will be announced in a detailed notice mailed on request.

For further information with regard to these various programs of postgraduate instruction kindly communicate with Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, Calif.

Award for Essay on Result of Research in Urology.—The American Urological Association offers an annual award "not to exceed $500" for an essay (or essays) on the result of some clinical or laboratory research in urology. The offer is limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals. Further information may be procured from the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tenn.

BEARING OF GENERAL NUTRITIONAL STATE ON ATHEROSCLEROSIS

SIGMUND L. WILENS, M.D.

NEW YORK

MUCH attention has been directed toward the role that specific nutritional factors may play in the development of atherosclerosis in man. For example, the influence of the cholesterol content of the diet and the blood has been studied in great detail. There are, however, a number of observations that indicate that the general nutritional state of a person may have an important bearing on the formation of the atherosclerotic lesions. These observations may be divided into two categories: (1) those suggesting that obesity favors rapid and extensive development of atheromatous plaques and (2) those indicating that prolonged undernutrition may retard the formation of such lesions.

Chief among the first group are the extensive statistics of insurance companies,[1] in which it is shown that important clinical consequences of atherosclerosis (e. g., occlusion of the coronary artery and cerebral hemorrhage) occur more commonly in obese persons than in persons of average nutrition or in the undernourished. The most plausible explanation of this finding is that the atherosclerotic process is more advanced in the obese group. The alternative explanation is that the lesions themselves may not be more severe in obese than in other persons but that the extra mechanical burden imposed on the cardiovascular system by excessive deposits of fat in the tissues may lead to greater impairment of function.

Diabetes mellitus and arterial hypertension are two conditions that are widely held to predispose to the development of atherosclerosis. There is considerable evidence that both occur more commonly in per-

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1. (a) Dublin, L. I.; Fisk, E. L., and Kopf, E. W.: Physical Defects as Revealed by Periodic Health Examinations, Am. J. M. Sc. **170**:576-594, 1925. (b) Britten, R. H.: Physical Impairment and Weight, Pub. Health Rep. **48**:926-944, 1933. (c) Dublin, L. I.: The Influence of Weight on Certain Causes of Death, Human Biol. **2**:159-184, 1930. (d) Dublin, L. I., and Marks, H. H.: The Build of Women and Its Relation to Their Mortality: A Preliminary Report, New York, Metropolitan Life Insurance Company, 1938; Mortality of Women According to Build: Experience on Substandard Issues, ibid., 1938. (f) Ideal Weights for Women, Statist. Bull. Metrop. Life Insur. Co. **23**:6, 1942. (g) Ideal Weights for Men, ibid. **24**:6, 1943.

sons who are overweight than in those who are underweight.[2] In Cushing's syndrome, in which obesity is coexistent with both diabetes and arterial hypertension, a tendency for severe atherosclerosis to develop has been noted.[3] The part that obesity itself may play in producing the arterial lesions in these disorders has not been clearly elucidated. Joslin[4] attributed the severe atherosclerosis of diabetic patients to the associated obesity. This view is not accepted by other observers.[5] In hypothyroidism and myxedema, in which both diabetes and arterial hypertension are generally absent, there is a tendency toward obesity. Severe atherosclerosis has been reported as frequent in this condition.[6] Severe atherosclerosis was reported by Kuczynski[7] to occur at an early age among nomads of the Kirghiz Steppes. A high incidence of obesity occurs in this population, due to consumption of unusually large amounts of food. French and Dock[8] reported that, of 80 young soldiers dying of coronary arteriosclerosis, 73 were overweight. Finally, the incidence of obesity increases progressively with age in much the same fashion as the incidence of atherosclerosis itself. This association may be merely one of coincidence, but the possibility exists that some of the increase in atherosclerosis with advancing age can be attributed to overnutrition.

In parts of the world where poor nutrition is prevalent, a low incidence of atherosclerosis has been reported. This appears to be particularly true of China and some of the Central American countries. In China Oppenheim[9] and more recently Snapper[10] observed little atherosclerosis even in persons dying at an advanced age. Similar observations have been reported in Costa Rica.[11] My observations in

2. Obesity and Diabetes, editorial, J. A. M. A. **95**:202 (July 19) 1930. Wyckoff, J.: The Treatment of Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 570.

3. Heinbecker, P.: The Pathogenesis of Cushing's Syndrome, Medicine **23**:225-247, 1944.

4. Joslin, E. P.: Arteriosclerosis and Diabetes, Ann. Clin. Med. **5**:1061-1080, 1927.

5. Wilder, R. M.: Diabetic Arteriosclerosis, Internat. Clin. **2**:13-20, 1939.

6. Fishberg, A. M.: Arteriosclerosis in Thyroid Deficiency, J. A. M. A. **82**:463-465 (Feb. 9) 1924. Bartels, E. C., and Bell, G.: Myxedema and Coronary Sclerotic Heart Disease, Tr. Am. A. Study Goiter, 1939, pp. 5-15.

7. Kuczynski, B.: Pathologische-geographische Untersuchungen in der Kirgesisch-dsungarischen Steppe, Klin. Wchnschr. **4**:39, 1925.

8. French, A. J., and Dock, W.: Fatal Coronary Arteriosclerosis in Young Soldiers, J. A. M. A. **124**:1233-1237 (April 29) 1944.

9. Oppenheim, F.: Review of One Hundred Autopsies of Shanghai Chinese, China M. J. **39**:1067-1076, 1925.

10. Snapper, I.: Chinese Lessons to Western Medicine, New York, Interscience Publishers, 1941, pp. 160 and 190.

11. Anitschkow, N.: Pathologische Anatomie und allgemeine Pathologie der Arteriosklerose, in Conférence internationale de pathologie géographique, Utrecht, 1934, pp. 44-97.

the latter country are in accord. At the Hospital San Juan di Dios in San José, Costa Rica, the majority of persons coming to necropsy are decidedly underweight. Ordinarily, no subcutaneous, mesenteric, omental, perirenal, peripelvic or epicardial adipose tissue is found. Even persons in the sixth and seventh decades at death usually have practically no atheromatous plaques in the aorta, the coronary arteries or other vessels. In China Oppenheim [9] noted that even in the presence of syphilitic aortitis there were no superimposed atherosclerotic plaques in the aortic intima. In the United States and Europe syphilitic aortitis and atherosclerosis are often coexistent. The view has been expressed that the syphilitic lesion ordinarily promotes the formation of intimal atheromatous plaques.

The low incidence of atherosclerosis in China is sometimes attributed to dietary factors [10] or to related arterial hypotension.[9] It is true that neither arterial hypertension nor diabetes is common in that country, but the degree of atherosclerosis noted at necropsy is apparently even milder than that observed as a rule in nonhypertensive and nondiabetic persons in the United States. The difference of mean systolic blood pressures in China and the United States is less than 10 mm. of mercury.[12] Therefore it seems doubtful that this slight difference could account for the variations in severity of atherosclerosis. It is also unlikely that specific dietary factors are involved. There is no reason to believe that two such divergent populations as the Chinese and the Costa Ricans consume exactly similar types of food.

Weiss and Minot [13] stated that there is some evidence that patients with chronic pulmonary tuberculosis may enjoy relative freedom from atherosclerosis. In such patients severe malnutrition is commonly present. In the examination of arteries of tuberculous patients at necropsies in the department of pathology at New York University little atherosclerosis has been found, particularly when severe undernutrition was present.

There has been no convincing demonstration that the state of nutrition is not related to the formation of atherosclerotic lesions. Rosenthal,[14] it is true, in an analysis of postmortem material found no relationship between body weight and degree of atherosclerosis, but his series included relatively few examples of obesity. It is also true that

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12. Tung, C. L.: Relative Hypotension of Foreigners in China, Arch. Int. Med. **40**:153-158 (Aug.) 1927.

13. Weiss, S., and Minot, S. R.: Nutrition in Relation to Arteriosclerosis in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, pp. 233-248.

14. Rosenthal, S. R.: Studies in Atherosclerosis. Chemical, Experimental and Morphologic: III. and IV. Roles of Cholesterol Metabolism, Blood Pressure and Structure of the Aorta; The Fat Angle of the Aorta (F. A. A.) and the Infiltration–Expression Theory of Lipoid Deposit, Arch. Path. **18**:660-698 (Nov.) 1934.

obesity is more prevalent in women than in men, yet clinical evidence of disease of the coronary or the cerebral arteries is less common in women. There is, however, no substantial proof that arterial lesions are less abundant in women. Rosenthal [14] found no striking sex difference in the incidence of atherosclerotic plaques.

It is not generally accepted that a relationship exists between nutrition and atherosclerosis. In a review on this subject written in 1933, Weiss and Minot [13] made the following statement: "There is no proof that overnutrition leads to atherosclerosis in man." In 1943 Wright [15] made essentially the same comment. There are a number of circumstances that make it difficult to establish a relationship between the two. Chief among these is the fact that the state of nutrition may fluctuate during different periods of a person's life. During many terminal illnesses there may be profound loss of weight. Prolonged periods of heart failure resulting from coronary arteriosclerosis itself may lead to striking depletion of fat deposits throughout the body. Obviously, the general state of nutrition in a given person is best evaluated during periods of health. However, the usual methods of measuring the extent of involvement of the arteries during life are unsatisfactory. Roentgenographic evidence of calcification of arteries may signify medial involvement in complete absence of the more important intimal lesions. For the same reason direct palpation of peripheral vessels may give erroneous impressions. Clinical evidence of impairment of the coronary, renal or cerebral circulation, if present, is a more reliable guide to the extent of the atherosclerotic process. But even this may be misleading. Postmortem examination may subsequently reveal a few plaques limited to isolated segments of the arterial system. These may be strategically located to cause striking impairment of function, but the clinical impression of widespread arteriosclerosis is not confirmed. Contrariwise, necropsy may reveal atherosclerosis throughout the arteries of persons who during life never exhibited any consequences of this disease.

Postmortem examination thus remains the most satisfactory method of determining the extent of atherosclerosis. However, the state of nutrition found at death may be the result of the terminal disease process, particularly if a chronic ailment such as tuberculosis, cancer or heart disease is present. Moreover, the clinical record as regards fluctuations in weight is frequently inadequate or unreliable. These defects complicate the evaluation of necropsy statistics when one tries to make accurate analyses of the relationship between nutrition and atherosclerosis, but they do not completely invalidate the use of such statistics, for the following reason: In practically all instances the state of nutrition at death will be either the same or poorer than it was prior to the

15. Wright, I. S.: Arteriosclerosis, in Stieglitz, E. J.: Geriatric Medicine, Philadelphia, W. B. Saunders Company, 1943, pp. 496-497.

onset of the final illness. There are few fatal illnesses that are associated with increased deposition of fat shortly before death. In other words, any change in nutrition that occurs with fatal disease is usually in one direction, namely, from a well nourished to a poorly nourished state. If this circumstance is taken into account, valid information can be obtained from the analysis of postmortem material.

If no relationship exists between nutrition and atherosclerosis and all other pertinent factors, such as age, sex, arterial hypertension and diabetes, are controlled, the incidence of atherosclerosis at autopsy should be about the same in obese, well nourished and poorly nourished groups. This will obtain no matter what the state of nutrition of the various persons in each of these groups may have been prior to the terminal illness. If a significant relationship does exist, variations in the incidence of atherosclerosis are to be expected in these three groups but will have to be interpreted with the effects of possible terminal changes in nutrition taken into account.

In the first place, the group that is found to be obese at necropsy will consist almost entirely of persons who were obese prior to the final illness. From this group will have been lost some who were formerly obese but who have lost considerable weight because of a cancerous growth, tuberculosis, severe arteriosclerosis itself or some other chronic disease process. There is no reason to believe that any selective loss of weight or absence of such loss will have occurred only in the obese persons with severe atherosclerosis. Therefore the degree of atherosclerosis found in those in whom obesity persists at the time of necropsy should be a fair approximation of the degree of atherosclerosis to be found in obese persons as a whole.

The group that is found to be within average limits of nutrition at necropsy will contain some members who were formerly obese and will have lost a large number of persons who, while of average nutrition for most of their lives, became malnourished shortly before death. If obesity favors the formation of atherosclerotic plaques, the addition of the formerly obese persons will increase the incidence of atherosclerosis in this group. If obesity retards the development of atherosclerosis, the opposite will hold true. In either case the difference in incidence of atherosclerotic lesions in truly obese and truly well nourished persons will be reduced by the inclusion of some formerly obese persons in the group with average nutrition as estimated at the time of death.

The group that is judged to be poorly nourished at the time of necropsy will contain some persons who were obese in health and a larger number who were of average nutrition prior to the final illness. If prolonged undernutrition retards the progression of atherosclerosis, the addition of these recently undernourished persons will raise the incidence of atherosclerosis in this group above that which actually obtains

in the presence of chronic undernutrition. If prolonged undernutrition increases the incidence of atherosclerosis, the opposite will hold true.

If both obesity and undernutrition have the same effect on the incidence of atherosclerosis—if, for example, both enhance the formation of atherosclerotic lesions—there will be some difficulty in the interpretation of the postmortem observations. The inclusion of a large number of previously normally nourished persons within the chronically undernourished group will lower the incidence of atherosclerosis below the true value. At the same time the introduction of a smaller group of formerly obese persons with a high incidence of atherosclerosis into the remaining group with average nutrition will raise the incidence of atherosclerosis slightly. In other words, the difference among all three nutritional groups as evaluated at necropsy will tend to be erased.

In each example cited, it will be noted that terminal loss of weight tends to reduce rather than to exaggerate or reverse any true differences in the incidence of atherosclerosis that might be related to the original state of nutrition. If such differences are not great, they may be entirely concealed by the changes that have occurred in the nutritional state as a part of fatal disease processes. It is possible that the failure to detect an obvious relationship between atherosclerosis and nutrition hitherto is explainable on this basis.

The study reported in this paper is based on findings in 1,250 necropsies performed at Bellevue Hospital, New York. Of these, 1,000 represent consecutive, unselected necropsies of persons 35 years of age or older at the time of death. Since they included an inadequate number of necropsies of obese persons, the series was enlarged by including the next consecutive 250 necropsies of persons 35 years of age or older who were obese.

MATERIAL AND METHODS

The series is divided into three groups according to the state of nutrition as evaluated at autopsy. The statement as to the general state of nutrition recorded in the protocol was generally accepted in making this classification. This was fortified by the estimated weight in comparison with the length and the general body build and also by the description of the deposits of fat found in various parts of the body. A measurement of the subcutaneous abdominal layer of fat was available in most instances, and a recent check indicates that this measurement is a good standard for evaluating the general state of nutrition. An abdominal panniculus 3 cm. or more in thickness was accepted as evidence of obesity. An abdominal subcutaneous layer of fat of less than 1 cm. when combined with depletion of deposits of fat in other parts of the body was accepted as an indication of poor nutrition. Some inaccuracy is unquestionably involved in this type of classification. This is probably particularly true in the group classified as being of average nutrition, since some of these may have been mildly overweight or underweight. The actual body weight was not available in many instances. This measurement by itself is not an infallible one in determining the state of nutrition unless one takes into consideration the body build and the degree of dehydration or of accumulation of excess fluids in the tissues and body cavities.

The patients of each nutritional group were reclassified by the degree of atherosclerosis present into the following categories: (1) those with no atherosclerotic lesions anywhere in the arterial system or only slight ones; (2) those with a moderate degree, and (3) those with severe and widespread lesions. Again the pathologist's estimate as recorded in the protocol was accepted. This simple method of measuring the extent of atherosclerosis is open to criticism, since it is based on the subjective interpretation of an unconcerned observer who in many instances made but casual reference to the condition of the arteries. The pathologist may be subconsciously influenced by the age or the clinical diagnosis in making an estimate of the extent of the atherosclerotic process. Lesions that in an elderly person would be called moderate in degree are sometimes called extensive if seen in a young person. If a clinical diagnosis of general arteriosclerosis has been made and if only a moderate degree is found at necropsy, the pathologist may be tempted to emphasize the discrepancy by calling the lesions rather mild. However, most of the grosser inaccuracies probably fall into the group classified as showing a moderate degree of atherosclerosis, since there is a wide range of lesions that may be so designated.

These data may be lacking in precision, but they at least have the virtue of having been recorded with complete detachment as regards a possible relationship between atherosclerosis and general nutrition.

As a further check, the incidence of atherosclerosis of the coronary arteries was tabulated separately. These vessels were chosen not only because they are frequently involved by atherosclerosis but also because they are examined at necropsy with considerable care. There are many instances in which there is a wide disparity between the degree of involvement of the coronary arteries by atherosclerosis and that of all other vessels. But the results obtained from analysis of the data on the incidence of atherosclerosis in relation to nutrition in each large group were essentially the same for the coronary arteries alone as for the arterial system as a whole. The data obtained from tabulations of the incidence of coronary arteriosclerosis will therefore be referred to in detail only when some noteworthy difference was observed.

RESULTS

Relation of Sex and Nutrition to General Atherosclerosis.—In table 1 is recorded the incidence of general atherosclerosis in men and in women

TABLE 1.—*Relation of Nutrition and Sex to General Atherosclerosis*

		Atherosclerosis						
		None or Slight		Moderate		Advanced		
	Nutrition	No.	%	No.	%	No.	%	Total
Men	Obese..........	39	23.1	62	36.7	68	40.2	169
	Average........	107	40.8	100	38.2	55	20.9	262
	Poor...........	173	47.1	136	37.1	58	15.8	367
Women	Obese..........	69	30.5	83	36.7	74	32.8	226
	Average........	53	48.2	34	30.9	23	20.9	110
	Poor...........	53	45.7	42	36.2	21	18.1	116

in each nutritional group. It may be noted that the incidence of atherosclerosis is practically identical in the sex subdivision of the poorly nourished group and that there is a higher incidence of severe atherosclerosis

in the sex subdivisions of the obese group. In obese men the incidence of severe atherosclerosis is two and a half times as great as in poorly nourished ones, and only one half as many of the obese men have little or no atherosclerotic change. In obese women the incidence of severe atherosclerosis is almost twice as high as in poorly nourished women. In every instance the incidence of atherosclerosis in the sex subdivisions with average nutrition is intermediate to the incidence in the obese and the incidence in the poorly nourished sex groups. In other words, the incidence of general atherosclerosis in a series of patients, if not in individuals, is directly proportional to the amount of adipose tissue deposited throughout the body. Obese women appear to have a somewhat lower incidence of severe atherosclerosis than obese men.

The incidence of atherosclerosis of the coronary arteries in relation to the state of nutrition is recorded in table 2. It will be noted that the incidence of atherosclerosis of these arteries alone, as was that of

TABLE 2.—*Relation of Nutrition and Sex to Coronary Atherosclerosis*

| | | Atherosclerosis | | | | | |
| | | None or Slight | | Moderate | | Advanced | | |
	Nutrition	No.	%	No.	%	No.	%	Total
Men	Obese..........	54	32.0	46	27.2	69	40.8	169
	Average........	123	46.9	90	34.4	49	18.7	262
	Poor..........	220	60.0	101	27.5	46	12.5	367
Women	Obese..........	92	40.7	83	36.7	51	22.6	226
	Average........	58	52.7	30	27.3	22	20.0	110
	Poor..........	69	59.5	33	28.4	14	12.1	116

general atherosclerosis, is approximately the same in the two sexes in the poorly nourished group. However, obesity in men appears to be a more important factor in increasing the incidence of atherosclerosis of the coronary arteries than obesity in women. The incidence of severe atherosclerosis is almost twice as high in obese men as in obese women. This suggests that other factors may be of importance in atherosclerosis of these particular vessels. For example, there may be some predisposing condition of the vessel wall in men that in the presence of obesity may favor the development of atherosclerosis. In all other respects the relationship between nutrition and atherosclerosis is essentially the same for the coronary artery by itself as for the arterial system as a whole.

Relation of Age and Nutrition to General Atherosclerosis.—The incidence of obesity increases with advancing age except in extreme old age. The relatively lower incidence of obesity late in life is due in part to the wasting and atrophy of tissues associated with senility and in part to the fact that the life span of obese persons is on the average shorter than that of persons of average nutrition or undernutrition.[1c] Nevertheless, it is possible that the relationship between nutrition and

atherosclerosis shown in tables 1 and 2 may be attributed to the inclusion of large numbers of old persons in the obese groups.

In table 3, in which the relationship of nutrition to general atherosclerosis is arranged by decades, this is shown not to be the case. The relationship within each decade is the same as that found for the entire series. The incidence of severe atherosclerosis is approximately two to four times as high in obese as in poorly nourished persons. It may be seen that the incidence of severe atherosclerosis is actually higher in the obese persons of 35 to 44 years than in the poorly nourished ones of 45 to 54 years. In fact, the incidence of severe atherosclerosis among the obese of any decade of life is greater than that among the poorly nourished persons of the succeeding age group. If the difference in incidence of atherosclerosis between obese and poorly nourished groups

TABLE 3.—*Relation of Age and Nutrition to General Atherosclerosis*

		Atherosclerosis						
		None or Slight		Moderate		Advanced		
Age, Yr.	Nutrition	No.	%	No.	%	No.	%	Total
35 - 44	Obese.........	26	55.3	17	36.2	4	8.5	47
	Average........	54	77.1	14	20.0	2	2.9	70
	Poor..........	52	89.7	5	8.6	1	1.7	58
45 - 54	Obese.........	41	46.1	30	33.7	18	20.2	89
	Average........	47	56.6	27	32.5	9	10.9	83
	Poor..........	50	56.2	33	37.1	6	6.7	89
55 - 64	Obese.........	27	22.9	47	39.8	44	37.3	118
	Average........	44	44.0	39	39.0	17	17.0	100
	Poor..........	69	46.3	56	37.6	24	16.1	149
65 - 74	Obese.........	11	11.6	41	43.1	43	45.3	95
	Average........	10	13.5	35	47.3	29	39.2	74
	Poor..........	46	37.1	53	42.7	25	20.2	124
75 and Over	Obese.........	3	6.5	10	21.7	33	71.8	46
	Average........	5	11.1	19	42.2	21	46.7	45
	Poor..........	9	14.3	31	49.2	23	36.5	63

be expressed in years, it may be said that obesity accelerates the development of severe atherosclerosis by about ten years. The figures in table 3 indicate that not only is the incidence of severe atherosclerosis high in obese persons but fewer obese persons escape with little or no atherosclerosis. With average nutrition the incidence of atherosclerosis is intermediate between that with obesity and that with poor nutrition. Within these two extremes the incidence of atherosclerosis appears to vary somewhat, so that in some instances it is close to that of obesity and in others close to that of poor nutrition. As already indicated, the age subdivisions designated as of average nutrition are more heterogeneous than those of the obese and the undernourished group, and less constancy is to be expected in the data derived from them.

Relation of Nutrition to General Atherosclerosis in the Nonhypertensive Group.—It is necessary to prove that the relationship between obesity and severe atherosclerosis indicated thus far is not influenced

by the inclusion of a large number of persons with hypertensive vascular disease in the obese group.   Some difficulty is encountered in establishing the presence or the absence of prolonged arterial hypertension in the persons of any necropsy series.   Many patients with hypertensive vascular disease are admitted to the hospital in shock or dying, and only low blood pressure readings are obtained.   Even more important is the fact that after attacks of occlusion of the coronary artery the blood pressure of persons who formerly had hypertension may fall to within normal limits.   In a few instances intracranial lesions may lead to a sudden elevation of blood pressure.   In tables 4 and 5 the incidence of atherosclerosis for each nutritional group of men and women deemed to be free from hypertensive vascular disease is shown.   The upper limits of normal blood pressure were placed at 150 systolic and 90 diastolic.

TABLE 4.—*Relation of Nutrition to General Atherosclerosis in Nonhypertensive Men*

		Atherosclerosis						
		None or Slight		Moderate		Advanced		
Age, Yr.	Nutrition	No.	%	No.	%	No.	%	Total
35 - 54	Obese..........	17	51.5	12	36.3	4	12.1	33
	Average........	46	63.0	23	31.5	4	5.5	73
	Poor...........	67	71.3	24	25.5	3	3.2	94
55 - 64	Obese..........	7	25.0	13	46.4	8	28.6	28
	Average........	26	50.0	20	38.5	6	11.5	52
	Poor...........	48	48.0	40	40.0	12	12.0	100
65 and over	Obese..........	2	6.7	13	43.3	15	50.0	30
	Average........	9	18.7	24	50.0	15	31.3	48
	Poor...........	39	32.2	53	43.8	29	24.0	121
Total, 35 and over	Obese..........	26	28.6	38	41.7	27	29.6	91
	Average........	81	46.8	67	38.7	25	14.5	173
	Poor...........	154	48.9	117	37.1	44	14.0	315

When one of these readings was slightly above and the other below the limit of normal and if cardiac hypertrophy was absent, the patient was classified as nonhypertensive.   It is admitted that a considerable and unknown number of formerly hypertensive persons are included among the terminally nonhypertensive groups.   It is unlikely, however, that the inclusion of these will alter the incidence of atherosclerosis to a great extent.

In men (table 4) the major observation is again confirmed, namely, that the incidence of severe atherosclerosis is considerably higher in persons who are obese than in persons poorly nourished, even when the known hypertensive persons are excluded.   This holds true in each of the age subdivisions shown.   An unexpected aspect is that up to the age of 65 the incidence of atherosclerosis in the nonhypertensive groups of average and poor nutrition is practically the same, whereas in those over 65 years of age the group with average nutrition has a higher incidence of atherosclerosis than has the poorly nourished group of

similar age. This suggests that in relatively young nonhypertensive men poor nutrition may not effectively retard or average nutrition enhance the development of atherosclerosis; on the other hand, hypertension may accelerate the development of atherosclerosis in relatively young men of average nutrition but may have little effect of this type in those of poor nutrition.

In nonhypertensive women (table 5) the difference in the incidence of atherosclerosis of the various nutritional groups is seen to be essentially the same as for men. In some of the age subgroups, in which the number of cases is relatively small, there is a certain amount of chance variation, but this is not enough to cast doubt on the validity of the major findings. The incidence of atherosclerosis is about the same in nonhypertensive women of average and of poor nutrition from 35 to

TABLE 5.—*Relation of Nutrition to General Atherosclerosis in Non-hypertensive Women*

Age, Yr.	Nutrition	Atherosclerosis						Total
		None or Slight		Moderate		Advanced		
		No.	%	No.	%	No.	%	
35 - 54	Obese	29	60.4	16	33.3	3	6.3	48
	Average	30	78.9	8	21.1	0	...	38
	Poor	24	77.4	6	19.4	1	3.2	31
55 - 64	Obese	11	30.6	16	44.4	9	25.0	36
	Average	6	46.1	4	30.8	3	23.1	13
	Poor	12	60.0	6	30.0	2	10.0	20
65 and over	Obese	5	13.9	14	38.9	17	47.2	36
	Average	3	11.5	13	50.0	10	38.5	26
	Poor	10	34.5	14	48.3	5	17.2	29
Total, 35 and over	Obese	45	37.5	46	38.3	29	24.2	120
	Average	39	50.6	25	32.5	13	16.9	77
	Poor	46	57.5	26	32.5	8	10.0	80

54 years of age. At more advanced ages those of average nutrition have a higher incidence than those of poor nutrition.

Relation of Arterial Hypertension and Nutrition to General Atherosclerosis.—In table 6 the relationship of nutrition to general atherosclerosis in the hypertensive groups is presented. Although all persons included in these groups had elevated blood pressure during their final illnesses, the duration of hypertension in many is not known. The difference in incidence of arteriosclerosis between obese and poorly nourished hypertensive persons is almost as great as between obese and poorly nourished nonhypertensive persons. Comparatively few poorly nourished women were found to have hypertension, particularly in the younger age groups. The incidence of atherosclerosis in these small groups probably has little statistical value. The incidence of severe atherosclerosis is found to be higher in hypertensive men with average nutrition than in those with poor nutrition. This is a point in contrast

to the findings in the nonhypertensive groups and supports the suggestion that hypertension may accelerate the development of atherosclerosis in both obese and average nutritional groups more than in poorly nourished ones.

By reference to tables 4 and 5 it may be noted, however, that the incidence of severe atherosclerosis is considerably higher in all hypertensive groups as compared with the corresponding ones without hypertension. It may be inferred, therefore, that the effects of hypertension in promoting the development of atherosclerosis are in good measure independent of the state of nutrition. In fact, all three factors that appear to be associated with the development of atherosclerosis—age,

TABLE 6.—*Relation of Hypertension and Nutrition to General Atherosclerosis*

| | Age, Yr. | Nutrition | Atherosclerosis | | | | | | Total |
| | | | None or Slight | | Moderate | | Advanced | | |
			No.	%	No.	%	No.	%	
Men	35 - 59	Obese.........	7	21.2	11	33.3	15	45.5	33
		Average.......	20	47.6	13	31.0	9	21.4	42
		Poor..........	11	42.3	11	42.3	4	15.4	26
	60 and over	Obese.........	6	13.3	13	28.9	26	57.8	45
		Average.......	6	12.8	20	42.5	21	44.7	47
		Poor..........	8	30.8	8	30.8	10	38.4	26
	Total, 35 and over	Obese.........	13	16.7	24	30.8	41	52.5	78
		Average.......	26	29.2	33	37.1	30	33.7	89
		Poor..........	19	36.5	19	36.5	14	27.0	52
Women	35 - 59	Obese.........	19	40.4	16	34.1	12	25.5	47
		Average.......	3	42.9	3	42.9	1	14.2	7
		Poor..........	5	50.0	3	30.0	2	20.0	10
	60 and over	Obese.........	5	8.5	21	35.6	33	55.9	59
		Average.......	11	42.3	6	23.1	9	34.6	26
		Poor..........	2	7.7	13	50.0	11	42.3	26
	Total, 35 and over	Obese.........	24	22.6	37	34.9	45	42.5	106
		Average.......	14	42.4	9	27.3	10	30.3	33
		Poor..........	7	19.5	16	44.4	13	36.1	36

obesity and hypertension—seem to operate independently of each other. In the presence of all three the incidence of severe atherosclerosis is particularly high. Three of every 5 obese hypertensive persons over the age of 60 have severe atherosclerosis; only 1 in 10 has slight atherosclerosis.

Relation of Heart Weight and Nutrition to General Atherosclerosis.— In some ways the weight of the heart at autopsy may be a more accurate measure of protracted hypertension than blood pressure readings obtained during periods of illness. But cardiac hypertrophy may result from other common conditions besides hypertensive vascular disease. These include valvular defects, myocarditis and the right-sided hypertrophy associated with pulmonary disease. Often systemic hypertensive vascular disease may be associated with these other types of heart disease, and it is difficult to determine how much the increase of weight of the heart is the result of the cardiac lesion and how much the result of the vascular

disease. Furthermore, even in the absence of hypertensive vascular disease and an intrinsic lesion of the heart, the weight of the heart varies considerably. At Bellevue Hospital it is not unusual to find hearts 450 Gm. in weight in large men in whom no evidence of hypertensive vascular disease has been elicited on repeated admissions to the hospital and in whom the heart shows no other abnormalities. Finally, it is possible to dissect away as much as 75 Gm. of adipose tissue from the epicardium of the obese subject.

Despite these drawbacks, most of which pertain to hypertrophied hearts, the incidence of atherosclerosis in each nutritional group is shown separately in table 7 for those persons with and without cardiac hypertrophy. This is done chiefly because it might be argued that enough persons who previously had arterial hypertension are inadvertently

TABLE 7.—*Relation of Heart Weight and Nutrition to General Atherosclerosis*

	Heart Weight, Gm.	Nutrition	Atherosclerosis						
			None or Slight		Moderate		Advanced		Total
			No.	%	No.	%	No.	%	
Men	Up to 400	Obese.........	9	37.5	8	33.3	7	29.2	24
		Average........	53	54.6	38	39.2	6	6.2	97
		Poor..........	135	52.9	91	35.7	29	11.4	255
	400 and over	Obese.........	30	20.7	54	37.2	61	42.1	145
		Average........	54	32.7	62	37.6	49	29.7	165
		Poor..........	38	33.9	45	40.2	29	25.9	112
Women	Up to 360	Obese.........	44	50.6	29	33.3	14	16.1	87
		Average........	33	53.2	22	35.5	7	11.3	62
		Poor..........	41	54.7	28	37.3	6	8.0	75
	360 and over	Obese.........	25	18.0	54	38.8	60	43.2	139
		Average........	20	41.7	12	25.0	16	33.3	48
		Poor..........	12	29.3	14	34.1	15	36.6	41

included among the obese nonhypertensive persons listed in tables 5 and 6 to raise the incidence of atherosclerosis in this group above the real value. The upper limits of normal heart weight are arbitrarily placed at 400 Gm. in men and 360 Gm. in women. No heart weights are excluded even when hypertrophy is obviously not the result of hypertension.

The main point under investigation is amply confirmed in table 7. There it may be seen that in both men and women without cardiac hypertrophy, and therefore presumably without prolonged arterial hypertension, the relative incidence of atherosclerosis in the obese group, the group of average nutrition and that of poor nutrition is about the same as indicated in tables 4 and 5, in which normal blood pressure readings obtained shortly before death were taken as the measure of absence of hypertension. It will be noted that the incidence of severe atherosclerosis is almost as high in the relatively small group of poorly nourished women with cardiac hypertrophy as in obese women with cardiac

hypertrophy.   Examination of the clinical records revealed that at least 4 of the 15 poorly nourished women with both cardiac hypertrophy and severe atherosclerosis had lost much weight in the last few months of life.   Inclusion of these among the small number of poorly nourished women with cardiac hypertrophy accounts for the falsely high incidence of severe atherosclerosis in this group.

Relation of Diabetes Mellitus and Nutrition to General Atherosclerosis.—The incidence of diabetes in persons 35 years of age or older on whom necropsy has been performed at Bellevue Hospital is only
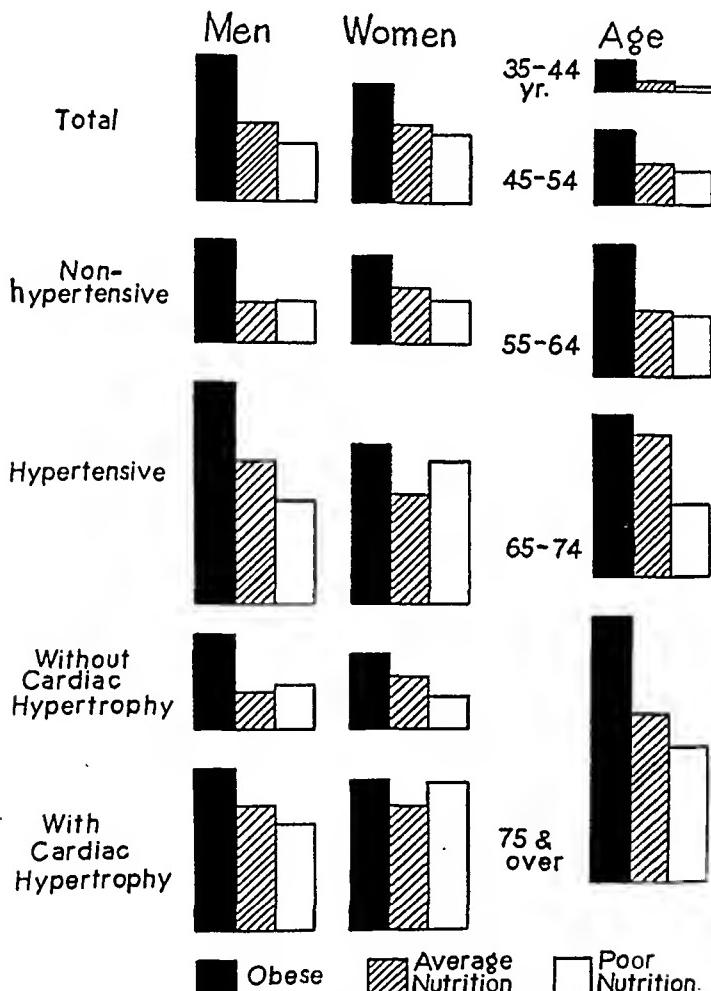
The relative incidence of severe atherosclerosis in obese persons, persons of average nutrition and poorly nourished persons as influenced by sex, age, blood pressure and heart weight.

about 4 per cent.   It is obvious that the inclusion of this small number among the 1,250 persons in this series will not appreciably alter the incidence of atherosclerosis in any one group.   Diabetes, however, is fairly common in obese persons.   Forty-two patients with diabetes (30 women and 12 men) are included among the 395 obese persons of

this series. Of these, 20, or almost 50 per cent, had severe atherosclerosis. If the diabetic group is omitted from the series, the incidence of atherosclerosis in nondiabetic obese men becomes: 23.7 per cent with little or no atherosclerosis, 37.8 per cent with moderate atherosclerosis and 38.5 per cent with severe atherosclerosis. Similarly, the incidence of atherosclerosis in nondiabetic obese women is: 33.3 per cent with little or no atherosclerosis, 35.9 per cent with moderate atherosclerosis and 30.8 per cent with severe atherosclerosis. Reference to table 1 will show that the incidence of atherosclerosis is not appreciably lower in obese nondiabetic persons than in the entire group of obese persons. It is still significantly higher in obese nondiabetic persons than in persons of average or pooor nutrition even if the diabetic persons are not excluded from the latter categories. It may be concluded therefore that the association demonstrated between obesity and severe atherosclerosis does not depend on the inclusion of diabetic persons in the obese group.

The relative incidence of severe atherosclerosis in each nutritional group as influenced by sex, age, blood pressure and heart weight is shown graphically in the chart.

COMMENT

It is an arresting fact that overweight is common in all the important conditions that are believed to be associated with the atherosclerotic process. The data furnished in this report indicate that overnutrition is in itself related to the development of atherosclerosis. There is also good evidence that poor nutrition may retard the formation of intimal lesions in old age and in the presence of hypertension. In nonhypertensive younger persons no difference in severity of atherosclerosis is observed in those of average and those of poor nutrition. The validity of the last observation is doubtful, as in both the latter groups the incidence of atherosclerosis has been artificially raised by the inclusion of formerly obese persons who became poorly nourished shortly before death.

From the figures cited in this report it would appear that obesity is less important than either high blood pressure or advanced age in promoting the development of atherosclerosis. However, it must be recalled that this study is based on the state of nutrition as observed at necropsy. It has already been indicated that the losses in weight that occur shortly before death will tend to reduce and conceal the nutritional factor in the incidence of atherosclerosis.

A crude estimate of the degree of nutritional change associated with fatal disease processes can be given. At death 30 per cent of the women over 35 years of age coming to autopsy at Bellevue Hospital are obese, 40 per cent are within average limits and 30 per cent are poorly nourished. A superficial survey of 1,500 visitors to the wards of Bellevue Hospital, who presumably were of the same background as the patients

themselves, indicates that, of middle-aged and elderly women, 60 per cent are frankly obese, 35 per cent within average limits and only about 5 per cent definitely underweight. These figures suggest that about one half of the obese women lose a large amount of weight before death and that undernutrition is six times as common among those who died. The nutrition of men over 35 years of age at autopsy is as follows: Only 10 per cent are obese; 40 per cent are of average nutritional status, and 50 per cent are poorly nourished. Corresponding figures for middle-aged and elderly male visitors to Bellevue Hospital are: 25 per cent obese, 65 per cent average and 10 per cent poorly nourished. In other words, more than half of the overweight group lose their obesity before death, and the incidence of poor nutrition is increased fivefold.

With these two sets of figures it is possible to estimate in a theoretic fashion the effects that change in nutrition at death might have on the true incidence of atherosclerosis as it is related to nutrition in health. For purposes of illustration, let it be assumed that 50 per cent of obese people, 25 per cent of persons with average nutrition and only 5 per cent of the undernourished over the age of 35 have severe atherosclerosis prior to illness. Let it be further assumed that two thirds of the obese people who lose weight because of wasting disease before death are brought by the loss of weight into the group with average nutrition and that in the remaining third the loss of weight has progressed to poor nutrition. In men the original true values of 50, 25 and 5 per cent of severe atherosclerosis in the respective groups will be altered by the weight changes to 50, 30 and 25 per cent. In women the same original values will be altered to 50, 38 and 30 per cent. In other words, a difference in incidence of severe atherosclerosis that was originally 10 to 1 between obese and poorly nourished persons has been reduced to 2 to 1 and 5 to 3.

This computation is based on the assumption that during a terminal period of a few months of poor nutrition no significant resorption or diminution of previously formed atherosclerotic lesions will occur. There is no evidence that the intimal plaques of adult human beings with atherosclerosis are reversible. It is likely, therefore, that the relationship between obesity and atherosclerosis is a much more striking one than the findings reported here indicate and that the state of nutrition is of great importance in the genesis of this disease.

It is obvious, nevertheless, that, like all the other factors known to be concerned in atherosclerosis, obesity is not essential for the development of the lesion. Almost 40 per cent of poorly nourished persons over the age of 75, from 30 to 40 per cent of all hypertensive persons with poor nutrition and even about 15 per cent of all poorly nourished nonhypertensive adults over the age of 35 have severe atherosclerosis at autopsy. It is not likely that the majority of these adults were ever

obese. Even when old age, hypertension and obesity are coexistent, almost 10 per cent may escape with little or no atherosclerosis.

It is also quite evident that obesity alone cannot be considered responsible for the development of atherosclerosis. This lesion is uncommon, for example, in obese persons under the age of 35. Even in older age groups, obese women appear to be less apt to have atherosclerosis than obese men. Finally, about one fourth of all obese persons over the age of 35 years show little or no atherosclerosis. Other conditions (e. g., predisposing changes in the arterial wall) must be fulfilled before overnutrition becomes a factor in the development of atherosclerosis, or one must suppose that there are different causes of obesity, only some of which are concerned in the atherosclerotic process. As a matter of fact, the data presented in this report merely confirm the existence of a relationship between nutrition and atherosclerosis; they do not afford any insight into the nature of this relationship. It might even be inferred that atherosclerosis leads to overnutrition, although this does not appear to be a plausible conjecture.

A certain amount of speculation over this relationship is perhaps justified. Newburgh [16] has shown that in obesity a disproportion between caloric intake and expenditure must inevitably be involved. In some instances of obesity the inadequate production of heat and energy due to sedentary habits or to intrinsic endocrine disturbances with lowered metabolic rate (e. g., hypothyroidism) may be chiefly concerned. In others excessive consumption of food is the predominant factor. It is likely that both excessive caloric intake and inadequate caloric expenditure are involved in many cases of obesity. Newburgh [16] finds that a relatively large consumption of food is required to maintain obesity. It is not inconceivable that the relationship between nutrition and atherosclerosis depends more on the excessive intake of food than on the amount of adipose tissue deposited throughout the body. The closer association between obesity and atherosclerosis in men than in women perhaps supports this contention, since the caloric requirements of men are generally stated to be higher than those of women. On the other hand, the association of atherosclerosis with myxedema and diabetes, since an excessive intake of food is not necessarily involved in these conditions, argues against this idea.

No matter what the cause of obesity may be in any individual case, it is logical that obesity involves the transportation of a large amount of fat from the alimentary canal to the tissues by way of the circulatory system. The development of atherosclerosis may conceivably result from a disturbance in this transportation. This is further supported by the

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16. Newburgh, L. H.: Obesity: I. Energy Metabolism, Physiol. Rev. **24**:18-31, 1944.

discovery of Hirsh and Weinhouse [17] that the lipids initially deposited in the arterial wall have the same composition as plasma lipid. In a certain sense atheromatous lesions when they occur in conjunction with obesity may be considered as modified deposits of fat in unusual locations.

It must be admitted that numerous investigations have failed to reveal a constant increase of lipid content of the plasma in persons who have atherosclerosis. Most of these investigations ignore the fact that the unrestricted ingestion of food may be followed by temporary periods of hyperlipemia. Hetenyi,[18] it is true, noted less hyperlipemia in obese subjects following a high fat test meal than in undernourished ones, but others [19] have found significant alimentary hyperlipemia in obese subjects. It is reasonable to infer that when the consumption of food is excessive the alimentary hyperlipemia will be more sustained and greater in degree than when the consumption of food is limited. Even if alimentary hyperlipemia is not associated with hypercholesteremia in obese subjects as was suggested by Blotner,[19b] but denied by Oppenheim and Bruger,[19c] one may suppose that the intimal surfaces of the arteries of obese persons are exposed to lipid-rich plasma for longer periods than are those of persons with average or poor nutrition. It is likely that the explanation of the association between obesity and atherosclerosis resides in this inference.

SUMMARY

In a comparison of the incidence of various degrees of general atherosclerosis and of atherosclerosis of the coronary arteries at necropsy in 395 obese persons, 372 persons of average nutrition and 483 poorly nourished persons 35 years of age and older it was found that advanced atherosclerosis is about twice as common in the obese as in the poorly nourished group. The group with average nutrition has less severe atherosclerosis than the obese group but more than the poorly nourished one.

Almost twice as many of the poorly nourished group as of the obese group have little or no atherosclerosis at necropsy. The incidence of little or no atherosclerosis in the group with average nutrition is intermediate between that of the poorly nourished and that of the obese group.

17. Hirsh, E., and Weinhouse, S.: Roles of Lipids in Arteriosclerosis, Physiol. Rev. **23**:185-202, 1943.

18. Hetenyi, G.: Untersuchungen über die Entstehung der Fettsucht, Deutsches Arch. f. klin. med. **179**:134-150, 1936.

19. (a) Rony, H. R., and Levy, A. J.: Studies in Fat Metabolism: I. Fat Tolerance in Obesity, J. Lab. & Clin. Med. **15**:221-228, 1929. (b) Blotner, H.: Blood Fat Tolerance Tests in Malnutrition and Obesity, Arch. Int. Med. **55**:121-130 (Jan.) 1935. (c) Oppenheim, E., and Bruger, M.: The Effect of a High Fat Test Meal on Blood Cholesterol in Normal and Obese Subjects, Am. J. M. Sc. **205**:77-82, 1943.

The relationship demonstrated between the state of nutrition at necropsy and the degree of atherosclerosis is independent of age, sex, hypertension, heart weight and diabetes. When the series is divided into subgroups according to age by decades, sex, absence or presence of terminal arterial hypertension, absence or presence of cardiac hypertrophy, the differences in incidence of atherosclerosis between the nutritional groups are essentially unchanged.

There is some indication that in nonhypertensive persons under 65 years of age the incidence of mild, moderate and advanced atherosclerosis in average and poorly nourished groups is about the same.

Obesity appears to be a more striking factor in the development of atherosclerosis in men than in women. This is particularly true of atherosclerosis of the coronary arteries.

Although the analysis is based on the state of nutrition as observed at necropsy, evidence is presented to show that if the analysis had been based on the probable state of nutrition prior to the onset of the final illness the relationship between atherosclerosis and nutrition would be even more striking.

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NECROSIS OF RENAL PAPILLAE AND ACUTE PYELONEPHRITIS IN DIABETES MELLITUS

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ACUTE necrosis of the renal papillae is one of the most conspicuous changes that may be seen in the kidneys of diabetic patients. It is a part of acute pyelonephritis, which may be fulminating in type. Papillary necrosis occurs also in nondiabetic persons with chronic urinary obstruction. Recovery is only occasionally seen. Although it is an important complication of diabetes, it has received little attention in the medical literature or textbooks, especially in America. As the condition has been only partially reviewed in the past, a more complete résumé seems pertinent.

The association of necrosis of the papillae and diabetes mellitus was first emphasized by Günther,[1] in 1937. However, as he mentioned, reports of the anatomic lesion as seen both in diabetic and in nondiabetic patients go back much further. Friedreich's[2] report in 1877 was apparently the first. His patient was a man of 70 years who had prostatic disease, hydronephrosis and bilateral papillary necrosis. Some of the necrotic papillae had separated from the pyramids and perhaps had been eliminated in the urine. Friedreich thought ·the process to be one of necrotic sequestration, independent of inflammation and caused by pressure atrophy due to stasis of urine, plus the possibility that flattening of the papillae might cause angulation of the blood vessels and deprivation of blood supply.

Turner[3] reported 3 cases from 1885 to 1888, one of which (1888) was that of an obese white woman of 60 who had diabetes mellitus and

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1. Günther, G. W.: Die Papillennekrosen der Niere bie Diabetes, München. med. Wchnschr. **84**:1695, 1937.

2. von Friedreich, N.: Ueber Necrose der Nierenpapillen bié Hydronephrose, Virchows Arch. f. path. Anat. **69**:308, 1877.

gangrene of the left foot. Stoudensky's [4] report of 6 cases in 1899 included 2 previously reported by Chiari.[4a] In all the papillary necrosis was associated with obstructive lesions of the urinary tract. Four of the patients had calculi, and 2 had hypertrophy of the prostate. Chiari considered mechanical twisting of the papillae as an etiologic factor. In 1928 Kaufmann,[5] in his textbook, described "diphtheria" or necrosis of the papillae and mentioned the fact that they may become detached and even occlude the ureter. Schömer [6] in 1931 reported the lesion as capillary metastatic necrosis of the renal medulla. Among the 3 patients, 1 was diabetic, a man of 48 with abscesses of the mandibular angle, later observed at necropsy to be due to an infection of the nasal sinuses with Friedländer's bacillus. Septic temperature and hematuria were present. Two patients were nondiabetic. One was a 68 year old woman with carcinoma of the stomach and bacteremia without a known focus. Bacterial thrombi in the capillaries of the renal medullae in and around the areas of necrosis were outstanding. The other was a 48 year old man with abcesses of the skin and ulcerative endocarditis of the aortic valve. Schömer called attention to a predilection of the necrotizing process for localization in the centers of the pyramids.

In 1934 Grauhan [7] presented a report of 2 cases in which there was a unilateral calculus obstruction leading to infectious necrosis of the entire kidney. One patient was a 52 year old woman; the other, a 41 year old man. Both were nondiabetic. He discussed the relationship of pyonephrosis and impaired circulation to the necrosis. In the same year Foulon and Busser [8] observed ischemic necrosis of the renal papillae of the lower pole of a kidney of which retrograde pyelograms had been made with the aid of 10 per cent "collargerol." In the upper pole was a hypernephroma. They considered that the disease was probably due to

3. Turner, F. C.: A Kidney from a Case of Phthisis, Showing Mortification of the Apices of the Pyramids, Tr. Path. Soc. London **36**:268, 1884-1885; Necrosis with Softening in Pyramids of the Kidneys: Recent Endo-Pericarditis (Card Specimen), ibid. **37**:290, 1886; Necrosis of the Pyramids of One Kidney, ibid. **39**:159, 1888.

4. Stoudensky, A.: Ueber die Nierenpapillennekrose bei Hydronephrose, Ztschr. f. Heilk. **20**:459, 1899.

4a. Chiari, H.: Mitt. d. Wien. med. Doct. Coll., 1882, vol. 8, no. 12; Ueber den anatomischen Befund einer zwanzig Tage alten, inter partum entstandenen, in Heilung begriffenen, completen Uterusruptur, Prag. med. Wchnschr. **24**:283, 1899.

5. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 2, p. 1364.

6. Schömer, W.: Capillarmetastatisch Marknekrosen der Nieren, Frankfurt. Ztschr. f. Path. **41**:265, 1931.

7. Grauhan, M.: Ueber die Entstehung von Pyonephrosen und entzündlichen Nierennekrosen, Ztschr. f. Urol. **28**:462, 1934.

8. Foulon, P., and Busser, F.: A propos des lésions rénales secondaires a la pyelographie rétrograde, Ann. d'anat. path. **11**:416, 1934.

compression of the blood vessels caused by the tumor, on one hand, and by distention of the pelves with collargol, on the other.

Günther [1] himself had observed the lesion in 10 specimens. Seven of these were from a series of 58 autopsies in which ascending suppurative pyelonephritis had been noted. Five of the 7 were from diabetic persons. Among 65 surgically removed pyelonephritic kidneys there were 3 with papillary necrosis complicating diabetes. Günther gave credit to Froboese for first emphasizing the relationship of papillary necrosis to diabetes mellitus. Froboese never published his observations. The same year Praetorius [9] observed "papillitis necroticans" in a 57 year old nondiabetic man. Also in 1937 Sheehan [10] reported a fatal instance of medullary necrosis of the kidneys in a nondiabetic 18 year old primipara in whom acute renal insufficiency developed post partum, associated with oliguria and arterial hypertension. She lived for nineteen days after the onset. Bacillus coli and staphylococci were present in the urine. At necropsy there was extensive necrosis of the papillae with commencing separation and microscopic healing at the line of demarcation. Sheehan expressed the belief that the necrotizing process, cutting across the collecting tubules, produced complete obstruction of the drainage of that segment; thus only small portions of unaffected renal tissue were able to function.

Alken's [11] report, in 1938, discussed 4 patients, all victims of diabetes mellitus and papillary necrosis, in 3 of whom the disease was unilateral and nephrectomy was performed. Only 2 of these were described in detail. One patient had complained of occasional fever and hematuria; a few days before admission to the hospital the patient had colicky pain, chills and high fever. There was almost complete loss of function of the left kidney, in contrast to normal function of the right. Retrograde pyelography revealed a large kidney with changes in the upper and the lower calices, composed of hazy outlines and irregular shapes. Nephrectomy was done and papillary necrosis noted. The other patient was a woman of 50 years whose chief complaint was hematuria. There was decreased function of the left kidney, Escherichia coli was present in the urine, and on a roentgenogram the contours of the upper calix were indistinct and contained a defect. The patient was treated conservatively but returned six months later because of renal colic of the left side. A papilla was passed in the urine, and the diagnosis of papillary necrosis was made histologically.

Alken emphasized the following points in clinical diagnosis: diabetes, decrease of renal function and roentgen findings, which are to be dis-

9. Praetorius: Papillitis necroticans bei schwerer chromischer Pyelonephritis, Ztschr. f. Urol. **31**:298, 1937.

10. Sheehan, H. L.: Medullary Necrosis of the Kidneys, Lancet **2**:187, 1937.

11. Alken, C. E.: Die Papillennekrose, Ztschr. f. Urol. **32**:433, 1938.

tinguished from those of tuberculosis and infiltrating tumor. However, the latter difficulty is present, as a rule, only in the early stages of papillary necrosis, when but one or two calices are involved. With advance of the disease and involvement of all papillae the evidence is against tuberculosis or neoplasm, which rarely involve all of the calices equally. He believed nephrectomy was indicated only in those patients in whom the disease was unilateral and of such severity that there was loss of renal function. With early diagnosis conservative treatment might be all that was necessary.

Mellgren and Redell [12] observed necrotizing pyelonephritis in 2 non-diabetic patients. One was a 63 year old woman who had had recurring bouts of pyelonephritis. Retrograde pyelography disclosed abnormalities of the calices on the left side. A contrast film revealed a mass which was thought to be a possible concretion. The involved kidney was explored and removed. Several days later symptoms referable to the right kidney developed, and the patient died several weeks later in uremia. In the left kidney at operation and the right kidney at autopsy there was diffuse papillary necrosis. The second patient was a 74 year old man who had prostatic hypertrophy, urinary retention and uremia. At necropsy there was a bilateral necrotizing papillary lesion. The blood sugar of this patient was normal.

The authors considered the predisposing cause to be deposition of a para-amyloid substance which acted to reduce the capillary blood supply, normally the poorest in the kidney. The precipitating cause, in their opinion, was a bacterial poison. In considering the relationship of diabetes to the disease, they thought that the deposition of a para-amyloid substance in the islets of the pancreas was similar to that in the renal papillae. In diabetic patients the para-amyloid substance, by pressure on vessels, would act as a special predisposing agent. They attached no importance to venous thrombosis. Among the characteristic roentgenographic changes, they included deformities and/or dilatation of the calices and separation of the papillary tips, leading to a mass of slough which might be called a concretion. Ring shadows in the roentgenogram were supposedly caused by sequestered papillae. The calices might communicate by small canals with the pelvis, simulating the appearance seen on the roentgenogram in renal tuberculosis.

Davson and Langley [13] published a report of a 28 year old woman with "papillitis renis necroticans" occurring as a terminal event in chronic pyelonephritis and uremia. There was no diabetes. In 1945

12. Mellgren, J., and Redell, G.: Clinical Pathology of Necrotizing Renal Papillitis, Acta chir. Scandinav. **84**:439, 1941.

13. Davson, J., and Langley, F. A.: Papillitis Renis Necroticans, J. Path. & Bact. **56**:327, 1944.

Eskelund [14] reported necrosis of the renal papillae following the use of a 25 per cent solution of sodium orthoiodohippurate for retrograde pyelography in a woman aged 55 who had acute and chronic pyelonephritis. In this country Harrison and Bailey [15] observed necrotizing pyelonephritis in 3 diabetic patients in whom there was no papillary necrosis.

In summation, then, papillary necrosis has been reported occurring in 13 diabetic and 20 nondiabetic persons, a total of 33. To this we add 50 unreported occurrences, 29 in diabetic and 21 in nondiabetic persons, bringing the total to 83.

As noted in foregoing paragraphs, there has been a lack of uniformity of opinion as to the proper nomenclature for this condition. The synonyms used include "papillary necrosis in hydronephrosis" (Friedreich [2]), "papillary necrosis of the kidney in diabetes mellitus" (Günther [1]), "papillitis necroticans" (Praetorius [8]), "diphtheria of the papillae" (Kaufmann [5]), "capillary metastatic necrosis of the renal medulla" (Schömer [6]), "necrotizing pyelonephritis" (Mellgren and Redell [12]) and "papillitis renis necroticans" (Davson and Langley [13]). As some choice has to be made by any author, we believe that the briefest descriptive term is best. At the Los Angeles County Hospital the resident staff has for a long time used the term "Günther's necrosis." Perhaps in due time Günther will be so honored. Only future authors can make that decision.

MATERIAL AND STATISTICS

For this report we have chosen our material from 859 necropsies of diabetic subjects (2.7 per cent) among 32,000 consecutive necropsies performed at the Los Angeles County Hospital between Sept. 23, 1924, and July 1, 1945. For comparison we have studied the acute infections of the kidneys in the remaining 31,141 nondiabetic subjects of the same necropsy series. We have not searched the surgical pathology records of the same period. In regard to material collected previous to 1941 we have depended on microscopic examination for diagnosis. Since that time we have personally supervised the collection of both gross and microscopic specimens. Among the 859 diabetic persons there were 107, or 12.4 per cent, in whom acute infection of one or both kidneys was the cause of death or contributed thereto. In this group of 107 with pyelonephritis there were 29, or 27.1 per cent, in whom a well circumscribed papillary to pyramidal necrosis was observed on gross or microscopic examination. In the remaining 78, necrotic areas were not seen in the papillae or, if present, involved only minor portions of one or more papillae. Minor degrees of renal infection were not included in this series of 107. There were 1,023 instances of acute pyelonephritis among the 31,141 nondiabetic subjects in the same series of 32,000 autopsies. In regard to

14. Eskelund, V.: Necrosis of Renal Papillae Following Retrograde Pyelography, Acta radiol. **26**:548, 1945; abstracted, J. A. M. A. **130**:1192 (April 20) 1946.

15. Harrison, J. H., and Bailey, O. T.: Significance of Necrotizing Pyelonephritis in Diabetes Mellitus, J. A. M. A. **118**:15 (Jan. 3) 1942.

the kidneys of 21 of these (2 per cent of the infected kidneys) we were able to make a diagnosis of papillary necrosis.

Certain inherent criticisms of such a study are obvious and should be mentioned. The gross descriptions of the disease recorded by the autopsy surgeons usually lacked sufficient detail for diagnosis previous to recognition of the process as an entity by the staff. Microscopic preparations of the kidneys often failed to include the papillae, even when the gross description would make one suspect necrosis. Sometimes no sections of kidney were .saved, so that we had to depend entirely on written descriptions of the histologic observations for a diagnosis of acute pyelonephritis. Since we used only those cases in which the lesion was seen in

TABLE 1.—*Apparent Increase in Incidence of Papillary Necrosis*

Necropsies	Diabetic Subjects	Number with Pyelonephritis	Number with Papillary Necrosis
1st 10,000..:	201	20	3
2d 10,000	226	33	7
3d 10,000	360	45	12
Last 2,000	72	9	7
Total	859	107	29

histologic preparations and relegated all others to the group of pyelonephritis without necrosis, the number of those with necrosis, for both diabetic and non-diabetic groups, is probably much too small. The incidence per 10,000 autopsies (table 1) supports this hypothesis. When carefully searched for, the lesion was noted in a much greater percentage than our statistics indicate.·

ACUTE NECROSIS OF RENAL PAPILLAE IN DIABETIC PATIENTS

Clinical Findings.—The clinical records of the 29 patients with necrosis of renal papillae are given in table 2 and summarized in table 3. In 26 patients (1 to 26 in table 2) the disease was of pyogenic origin. In 1 patient (27) healing had occurred, and in the remaining 2 (28 and 29) tuberculosis and actinomycosis, respectively, were the cause of the necrosis.

In attempting to analyze the data on the 26 patients with papillary necrosis of pyogenic origin it is noted that they can be divided into three groups, although there is some overlapping. In one group of patients there was a focus of infection elsewhere than in the urinary tract which resulted in septicemia and secondary involvement of the kidney. The second group consisted of diabetic patients whose renal lesion was the apparent result of infection confined to the urinary tract. The third group included those patients who entered the hospital in coma, presumably due to the papillary necrosis, and usually in uremia with or .without diabetic acidosis, and who died after only a few days during which their disease followed a fulminating course. Detailed summaries of the observations on 1 patient from each group follow.

In group 1 (renal involvement secondary·to infection elsewhere) there were 7 patients.

Patient	Age, Yr.	Sex	Cause of Entry to Hospital	Time in Hospital Before Death	Duration of Diabetes in Years	Complicating Diseases	Bacteriologic Results *	Carbon Dioxide Combining Power †
						Acute Papillary Necrosis		
1	35	M	Coma; hematemesis	14 hr.	13	Peptic ulcer; severe diabetic retinitis	....	32
2	42	F	Burns of legs; peripheral neuritis	10 mo.	13	Carbuncle; hypertension; chronic pyelonephritis	P. M. kidney: Beta strep.	..
3	62	F	Cellulitis of arm; gangrene of foot	5 mo.	12	....	P. M. kidney: gram-positive cocci on smear	..
4	71	F	Diabetes	25 days	20	Hypertension	....	..
5	43	F	Bacillary dysentery; diabetic acidosis	1½ mo.	New	....	Blood: negative; P. M. kidney: E. coli	..
6	51	M	Cirrhosis with ascites; hiccup	2 days	6	Generalized edema (Kimmelstiel-Wilson disease)	....	..
7	49	F	Diabetic coma	3 mo.	New	Abscess of thigb	Urine: E. coli; P. M. kidney: E. coli, alpha strep.	..
8	81	F	Coma	6 days	New	Generalized arteriosclerosis	....	46
9	50	F	Urinary symptoms	2½ mo.	1	....	Blood: E. coli; Urine: E. coli; P. M. kidney: B. proteus	..
10	41	M	Carbuncle; diabetic coma	7 wk.	9	....	Blood: Staph. aureus	58
11	72	M	Coma	3 days	13	Prostatic hypertrophy; chronic pyelonephritis	Blood: negative	55
12	63	F	Convulsions	2½ days	Several	Hypertension	P. M. kidney: E. coli	59
13	55	E	Stupor	7 days	10	Hypertension, mild	....	52
14	53	F	Diabetic coma; chills and fever	4 days	New	....	P. M. kidney: E. coli	13
15	62	M	Urinary retention	4 mo.	1	Prostatic hypertrophy; paralysis of bladder due to injury of cord; perirectal and cutaneous abscesses; alcoholism	Blood: Staph. aureus	..
16	63	F	Urinary symptoms	5 days	10	Hypertension	....	44
17	53	F	Diabetic acidosis	2 mo.	New	....	P. M. kidney: E. coli	36
18	74	M	Urinary retention (prostatic hypertrophy)	14 days	?	Auricular flutter	....	49
19	63	F	Carbuncle	6 days	1	....	Blood: negative P. M. kidney: Staph. aureus	53
20	63	F	Coma	12 days	3	Hypertension	P. M. kidney: Staph. aureus	..
21	53	F	Diabetic acidosis; gangrene of toes	5 days	New	Hypertension, mild	P. M. kidney: E. coli	24
22	68	F	Hematuria	5 days	14	Old hemiplegia; amputation of toe	P. M. kidney: E. coli, alpha strep.	55
23	54	M	Generalized edema (Kimmelstiel-Wilson disease)	14 days	6	....	P. M. kidney: Staph. aureus	45
24	59	F	Diabetes	17 days	New	....	P. M. kidney: Pseudomonas aerogenes, alpha strep.	50
25	53	F	Diabetic coma	10 days	New	Gangrene of toes; pneumonia	....	16
26	46	M	Coma (uremic) due to chronic pyelonephritis (urethral stricture)	1 day	New	Meningovascular syphilis	P. M. kidney: E. coli	30
						Healed Papillary Necrosis		
27	81	M	Diabetes; shortness of breath (Kimmelstiel-Wilson disease)	3½ mo.	New	Infected ulcer on leg	....	..
						Granulomatous Lesions with Papillary Necrosis		
28	57	M	Urinary symptoms; diabetes	32 days	5	Severe malnutrition	....	..
29	59	F	Urinary symptoms	3 mo.	New	....	Blood: negative Urine: negative for acid-fast bacilli	..

* P. M. kidney means postmortem culture of kidney.
† Carbon dioxide combining power is expressed in volumes per cent, taken within fourteen days of death.
‡ Nonprotein nitrogen is expressed in milligrams per hundred cubic centimeters of blood, taken within fourteen days of death.

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Nonprotein Nitrogen ‡	Albumin	White Blood Cells	Red Blood Cells	Treatment of Renal Lesion	Gross Pathologic Changes
		Urine Microscopic §			

Acute Papillary Necrosis

Nonprotein Nitrogen ‡	Albumin	White Blood Cells	Red Blood Cells	Treatment of Renal Lesion	Gross Pathologic Changes
212	...	...	...	....	Unilateral papillary necrosis with cortical abscesses; chronic pyelonephritis of opposite kidney
...	1+	4+	4+	....	Bilateral papillary necrosis with partial sloughing and healing; chronic pyelonephritis (?); carbuncle; epidural spinal abscess; pulmonary abscesses
...	3+	...	...	....	Bilateral papillary necrosis; no cortical abscesses; mild cystitis
...	1+	4+	...	"Urinary antiseptics"	Bilateral papillary necrosis; extensive cortical abscesses; purulent cystitis
...	2+	4+	...	....	Unilateral papillary necrosis; bilateral pyelonephritis; acute cystitis and ureteritis; bilateral pyosalpinx and pelvic abscesses
...	2+	4+	Rare	....	Bilateral papillary necrosis; no cortical abscesses; prostatic hypertrophy; uropathy due to infection and obstruction; portal cirrhosis
57	1+	4+	...	Ureteral catheters; "urinary antiseptics"	Unilateral papillary necrosis and chronic pyelonephritis due to ureteral kink
50	1+	4+	...	....	Unilateral papillary necrosis and pyonephrosis due to ureteral kink; no cortical abscesses
248	1+	4+	...	Ureteral catheters; sulfanilamide	Bilateral papillary necrosis with sloughing; perirenal inflammation; acute cystitis and ureteritis; weight of kidneys, 600 Gm.
...	2+	4+	4+	Sulfapyridine and sulfadiazine	Bilateral papillary necrosis with abscesses throughout kidneys; carbuncle of neck; cellulitis of leg
70	1+	...	...	....	Unilateral papillary necrosis; no cortical abscesses; benign hypertrophy of prostate with obstruction
150	1+	4+	...	....	Bilateral papillary necrosis with cortical abscesses; acute cystitis and ureteritis
230	Trace	1+	...	Ureteral catheters; sulfathiazole	Bilateral papillary necrosis; acute ureteritis; coronary sclerosis; myocardial scars; hirsutism of face; adrenal hyperplasia; nodular goiter; bronchopneumonia
48	...	1+	...	....	Unilateral papillary necrosis with small early cortical abscesses; mild acute ureteritis and cystitis; bronchopneumonia
93	4+	4+	4+	Retention catheter; sulfathiazole	Bilateral papillary necrosis; no cortical abscesses; benign hypertrophy of prostate; gangrene of skin of heels and back; osteomyelitis of clavicle; prostatic abscesses with rupture into rectum
115	Trace	4+	...	Sulfathiazole	Bilateral papillary necrosis with cortical abscesses
50	1+	2+	...	....	Bilateral papillary necrosis with solitary abscess in cortex; femoral thrombophlebitis; cerebral softening
...	0	4+	4+	Retention catheter	Bilateral papillary necrosis; few abscesses in cortex; benign hypertrophy of prostate with obstruction; bronchopneumonia
35	3+	4+	1+	Sulfadiazine	Bilateral papillary necrosis with no abscesses in cortex; carbuncle of skin; lateral sinus thrombosis; pulmonary embolism
...	0	4+	1+	Sulfathiazole	Bilateral papillary necrosis with cortical abscesses; acute pancreatitis; facial hirsutism
87	...	...	...	....	Bilateral papillary necrosis with thrombosis of renal veins; gangrene of foot
85	...	...	4+	Retention catheter; "urinary antiseptics"	Bilateral papillary necrosis without cortical abscesses; chronic cystitis; severe coronary arteriosclerosis; recent myocardial infarction
75	1+	4+	Rare	....	Bilateral papillary necrosis with cortical abscesses; acute cystitis; hydrothorax
26	2+	4+	...	Penicillin	Unilateral papillary necrosis with cortical abscesses; bilateral perinephritic abscesses; coronary arteriosclerosis; recent myocardial infarction
112	Trace	4+	...	....	Bilateral papillary necrosis with 0.5 mm. cortical abscesses; early ulcerative cystitis; mild acute ureteritis; gangrene of toes
60 to 100	1+	4+	1+	....	Bilateral papillary necrosis with cortical abscesses; urethral stricture with obstruction; acute cystitis and ureteritis

Healed Papillary Necrosis

Nonprotein Nitrogen ‡	Albumin	White Blood Cells	Red Blood Cells	Treatment of Renal Lesion	Gross Pathologic Changes
45	4+	4+	...	Sulfathiazole	Healed lesion of papillae; benign hypertrophy of prostate with obstruction; pulmonary tuberculosis; pulmonary edema; coronary sclerosis

Granulomatous Lesions with Papillary Necrosis

Nonprotein Nitrogen ‡	Albumin	White Blood Cells	Red Blood Cells	Treatment of Renal Lesion	Gross Pathologic Changes
....	1+	4+	...	Bladder irrigations; sulfathiazole	Unilateral papillary necrosis; hypertrophy of prostate with acute cystitis; tubercles of spleen
109	1+	4+	1+	....	Papillary necrosis of remaining kidney with small cortical abscesses; pyoureter and pyonephrosis

(In many instances the carbon dioxide combining power and nonprotein nitrogen were not determined within one or two days of death.)

§ 4+ means loaded with white blood cells or red blood cells.

A white man of 41 years (10 in table 2) entered the hospital on Nov. 16, 1938, in a semistuporous state. Diabetes had been discovered eleven years previously (1927) and treated for one year with 27 units of regular insulin. Thereafter he took no insulin and followed no diet. He claimed that he had felt well until a few months before entry, when he noted increased thirst and appetite and frequency of urination. Fifteen days prior to hospitalization a "pimple" developed on the back of his neck, which gradually increased in size. Three days before entry it was incised and drained. After this he felt weak, confused and short of breath.

Physical examination revealed an acutely ill, semicomatose man with respiration of the Kussmaul-Kien type and acetone breath. The temperature was 98 F.; the pulse rate, 104; the blood pressure, 100 mm. of mercury systolic and 70 diastolic; the respiratory rate, 22. There was a large carbuncle on the posterior aspect of the neck, with induration extending from the angle of the left jaw to the right posterior aspect of the neck and from the occiput to below the base of the neck. The remainder of the examination disclosed nothing remarkable.

After twenty-four hours of rigorous therapy with insulin and fluids for diabetic acidosis, cautery excision of the carbuncle was done on November 17. Pus was found deep in the neck under the trapezius muscle. As the lesion spread, a more extensive cautery excision (7 inches [18 cm.] in diameter) was performed on November 22. Abscesses appeared on the buttocks and the left ankle, and cellulitis of the left side of the face and left ear developed. The lesions all required surgical incision. Staphylococcus aureus was grown on culture of material from the abscess of the ankle. On December 21 the patient complained of pain in the left upper quadrant of the abdomen, where an indefinite mass was palpated. The bladder was distended at this time, with overflow incontinence, and the urine was loaded with red and white blood cells. He received seven transfusions of 250 cc. each of whole blood. He also received a total of 50,000 units of staphylococcus antitoxin intravenously on December 8 and 9. This treatment was not continued, because of a severe reaction. About 80 Gm. of sulfapyridine was given between December 31 and Jan. 3, 1939. Despite these measures the patient became weaker, pulmonary edema developed and death occurred on January 4, one and a half months after the patient entered the hospital. Throughout the hospital stay the temperature varied between 99 and 101 F. daily. The diabetes was never well controlled, despite the use of 100 to 130 units of insulin daily (regular and protamine zinc insulin). During the last two days of life the blood culture was positive for Staph. aureus. The output of urine remained unchanged throughout. The nonprotein nitrogen level was not determined.

The onset of pyelonephritis as a complication of sepsis was evident in this patient two weeks before death. Sulfapyridine was given for only four days. In retrospect no special clinical symptoms point to the beginning of the papillary necrosis complicating the pyelonephritis.

In group 2 (infection primary in the urinary tract) there were 12 patients.

A 50 year old woman (9 in table 2) entered the hospital on Oct. 4, 1938, with a history of weakness following bronchopneumonia one and a half years previously. She had been told in the year prior to entry that she had diabetes, and was treated with regular (?) insulin—5 to 10 units, one to two times daily—for three months without relief. Later she had been told that she did not have diabetes by a chiropractor who gave her electrotherapy treatments directed to the kidneys. A loss of 51 pounds (23 Kg.) and tingling of the feet had occurred over a period

of one year. Seven days before entry she noted chills, fever, and pain, which was dull and constant, in the left upper quadrant of the abdomen. With this there was urination every two or three hours, accompanied by slight burning. She had had "pink urine" (which she thought to be blood and pus) for one day.

On physical examination this patient was a well developed but emaciated middle-aged woman who appeared weak and chronically ill. The temperature was 98.6 F.; the pulse rate, 96; the respiratory rate, 30; the blood pressure, 84 mm. of mercury systolic and 45 diastolic. The tongue was red, dry and smooth. The heart and the lungs were not remarkable. The abdomen was obese and distended. Tenderness on deep pressure was noted in the left upper quadrant, where an indefinite mass could be felt. There was also tenderness in the left costovertebral angle. The pelvic examination gave essentially normal results.

On October 10 retrograde pyelograms showed a normal right renal pelvis. On the left there was irregular constriction of the renal pelvis and calices, with dilatation of a few minor calices. The superior calices, major and minor, showed generalized constriction and some apparent elongation.

Cystoscopic examination was performed, and ureteral catheters were inserted in the right and left renal pelves to remain for periods of four to nineteen days on five occasions from October 9 to the time of death on December 15. She received two courses of treatment with sulfanilamide, one of three days and one of nineteen days, supposedly 90 grains (5.8 Gm.) a day, but she frequently refused the medicine. The diabetes was easily controlled by diet, with no insulin or with small doses of regular insulin (10 units, two times daily). When she entered the hospital, her temperature was 103.8 F. but dropped to 101 the next day and then became low grade for the next two weeks. On both October 20 and 22 she had a chill, associated with a rise of temperature to 102 F. During the last two or three weeks of life her temperature was normal. In the last week of life she was weak and ate poorly. The volume of urine was not accurately charted but was reduced to 200 to 400 cc. per twenty-four hours during the last few days of life.

The laboratory examination on entry disclosed a leukocyte count of 18,850, with 93 per cent neutrophils, and a nonprotein nitrogen level of 124 mg. per hundred cubic centimeters of blood. With ureteral catheterization the nonprotein nitrogen level dropped to 60 mg. on October 17, only to rise again slowly over the course of two months to a terminal level of 248 mg. Throughout the course of the disease variable amounts of casts, erythrocytes, leukocytes and E. coli were noted in the urine.

Despite the early diagnosis of the pyelonephritis and its vigorous treatment, the patient failed to respond. The roentgen findings on October 10 suggest the onset of papillary necrosis early in the disease, which may explain the poor therapeutic results.

In group 3 (coma due to papillary necrosis) there were 7 patients.

A 63 year old woman (12 in table 2) entered the hospital in deep coma on Jan. 17, 1941 and died two and a half days later. The only history available was that of diabetes of many years' duration. She had not followed a diet well and had taken no insulin. There had been a loss of weight of 40 to 50 pounds (18 to 22.5 Kg.) in a few months. Five days prior to entry she contracted what she termed "influenza," with high fever, loss of appetite and polyuria.

The physical examination revealed a deeply comatose middle-aged woman. Her temperature was 101.6 F. rectally; the pulse rate, 140; the respiratory rate, 40; the blood pressure, 140 mm. of mercury systolic and 110 diastolic to 170 mm.

systolic and 90 diastolic. The heart, the lungs, the abdomen and the pelvic organs were without abnormality.

The urine contained albumin (2+), many pus cells and sugar (4+) but no acetone. The hemoglobin content of the blood was 95 per cent; the erythrocyte count was 4,500,000, and the white blood cell count, 14,800. The carbon dioxide-combining power was 29 volumes per cent on entry and rose to 59 on the second hospital day. The nonprotein nitrogen was 137 mg. per hundred cubic centimeters of blood.

The fulminating course in the presence of coma and evidence of pyelonephritis is characteristic of this group. The rapid course emphasizes the importance of the urinary findings and prompt treatment.

Roentgenologic Findings.—Retrograde pyelograms were taken in 4 cases. In 1 (9 in table 2) the pyelogram of the left side showed an irregular constriction of the renal pelvis and calices, with some dilation

Fig. 1.—The pelvic and calicine systems are well filled. There are two major calices. The minor calices exhibit erosion along the borders of their proximal outline, with a small amount of extravasated dye extending into the cortex of the kidney (patient 13 in table 2).

of a few of the minor ones. There was also general constriction of the superior calices, major and minor, with some apparent elongation. This was considered consistent with pyelonephritis except for the elongation, which suggested renal tumor or abscess. The pyelogram made of the right side on entry was normal. In 1 patient (29 in table 2) the minor calices showed irregularity and destruction. M. B. (7 in table 2) had, as shown by retrograde pyelography, an enlarged right kidney with little opaque medium beyond the region of the ureteral-pelvic junction. The appearance was suggestive of a renal tumor. The urogram of the left side was normal. Figure 1 illustrates the changes in the kidney in the fourth patient (13 in table 2), in which there was erosion of the

minor calices, with a small amount of extravasated dye extending into the cortex of the kidney.

These four studies illustrate the varied types of pyelograms which may be seen, from that of uncomplicated pyelonephritis to that of the ragged, moth-eaten stage of pyramidal necrosis, which has heretofore been associated only with renal tuberculosis. In 2 cases renal tumor was suggested because of renal enlargement or because of distortion of the calicine pattern with elongation.

Pathologic Observations.—Gross Examination: The disease was bilateral in 18 patients and unilateral in 8. In 2 of the latter group the changes were due to hypertrophy of the prostate; in 2 they were

Fig. 2.—Acute necrosis of the renal papillae with extension into the pyramids (patient 14 in table 2). Note that in the uppermost pyramid the necrosis extends almost to an arcuate artery. The renal pelvis is not greatly inflamed. A moderate number of small abscesses are present in the cortex. The reproduction is three-fourths actual size.

secondary to ureteral strictures, and in 1, to a pelvic abscess complicating pyosalpinx. Certain gross features are of interest. The dirty gray–yellow necrotic papillae stood out in striking contrast to the remainder of the renal parenchyma (fig. 2). The shape of the necrotic area was most often that of a segment of a circle, the rounded to flame-shaped base being not far from the limits of the pyramids but rarely reaching the arcuate artery. Thus a major portion of the pyramid might be necrotic. Each radial side of the necrotic area, as a rule, formed a straight line from the papillary-calicine angle and never

encroached on the renal column of Bertin. In less advanced lesions (3 cases) the necrotic areas involved only the tips of the papillae or were centrally located and had an irregular, serrated configuration parallel with the long axes of the collecting tubules. A diffuse involvement of all of the papillae was noted in one or both kidneys in all of the cases in which we made a gross examination. In regard to the older material, in the diagnosis of which we depend principally on microscopic examination alone, this point cannot be settled. The gross appearance of the remainder of the kidney varied greatly. In about a third of the cases no abscesses were seen in the cortex; in a majority (18 cases) abscesses measuring 1 to 2 cm. in diameter were present. Widespread necrosis of the cortex was seen only once.

In patients with sepsis secondary to a focus other than one in the urinary tract producing descending pyelonephritis, the pelvis and calices were only mildly hyperemic. Even with ascending infections the degree

Fig. 3.—Three stages of papillary necrosis. A, acute necrosis (patient 22 in table 2); × 4. B, sequestration of papillae (patient 22 in table 2); × 4. C, papillae eliminated (patient 2 in table 2); × 4.

of pyelitis seemed grossly out of proportion when compared with the degree of necrosis of the papillae (Günther[1] emphasized this point) except in 2 instances in which there was ureteral obstruction. Severe cystitis was noted only once. Thus the gross findings in one group suggested that what began as a mild, relatively symptomless infection of the lower urinary tract suddenly was converted into a highly fatal disease when it reached the papillae.

Microscopic Examination: Necrosis of the papillae was complete except in the 3 cases mentioned in a foregoing paragraph. In addition, from two thirds to three fourths of the pyramids were likewise involved, usually to a uniform depth, but occasionally the margin of the necrotic zone was irregular. In nearly all of the group the necrotic process had apparently advanced to about the same stage when death occurred. However, in the kidney of one patient (3, table 2) sequestration had

begun, and in that of another (26, table 2) many of the papillae had been cast off, even though other papillae were still attached. The three stages which may occur—i. e., necrosis, sequestration and elimination —are illustrated together (fig. 3). Within the areas of necrosis an
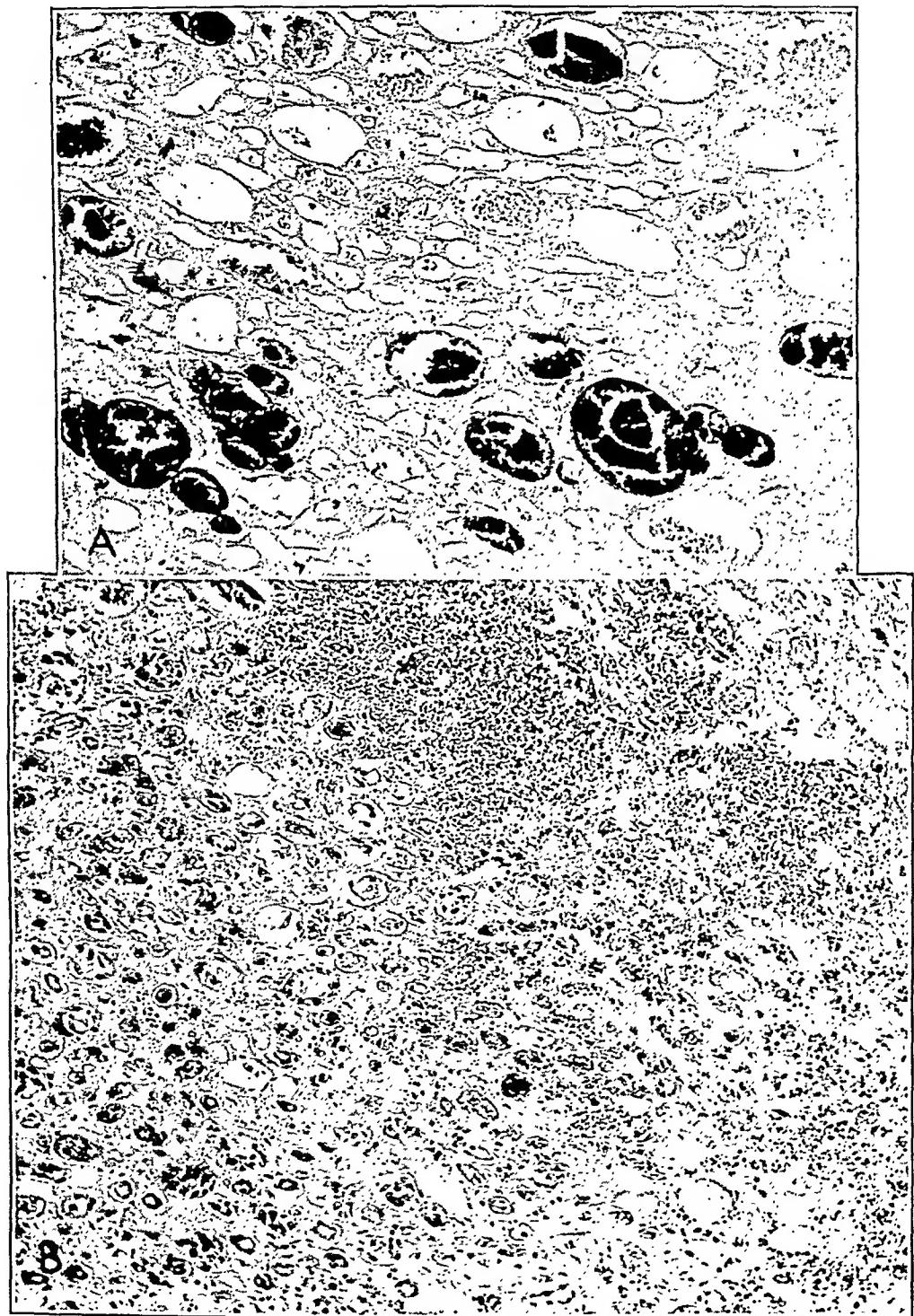
Fig. 4.—*A*, necrotic tubules filled with dark masses of organisms (patient 23 in table 2); × 150. *B*, absence of interstitial cellular exudate at margin of necrotic zone (patient 22 in table 2); × 185.

outstanding feature of the lesions caused by staphylococci was the tubules filled with blue-staining organisms (fig. 4 *A*), described by Günther.[1] The base of the necrotic area, with one exception, was
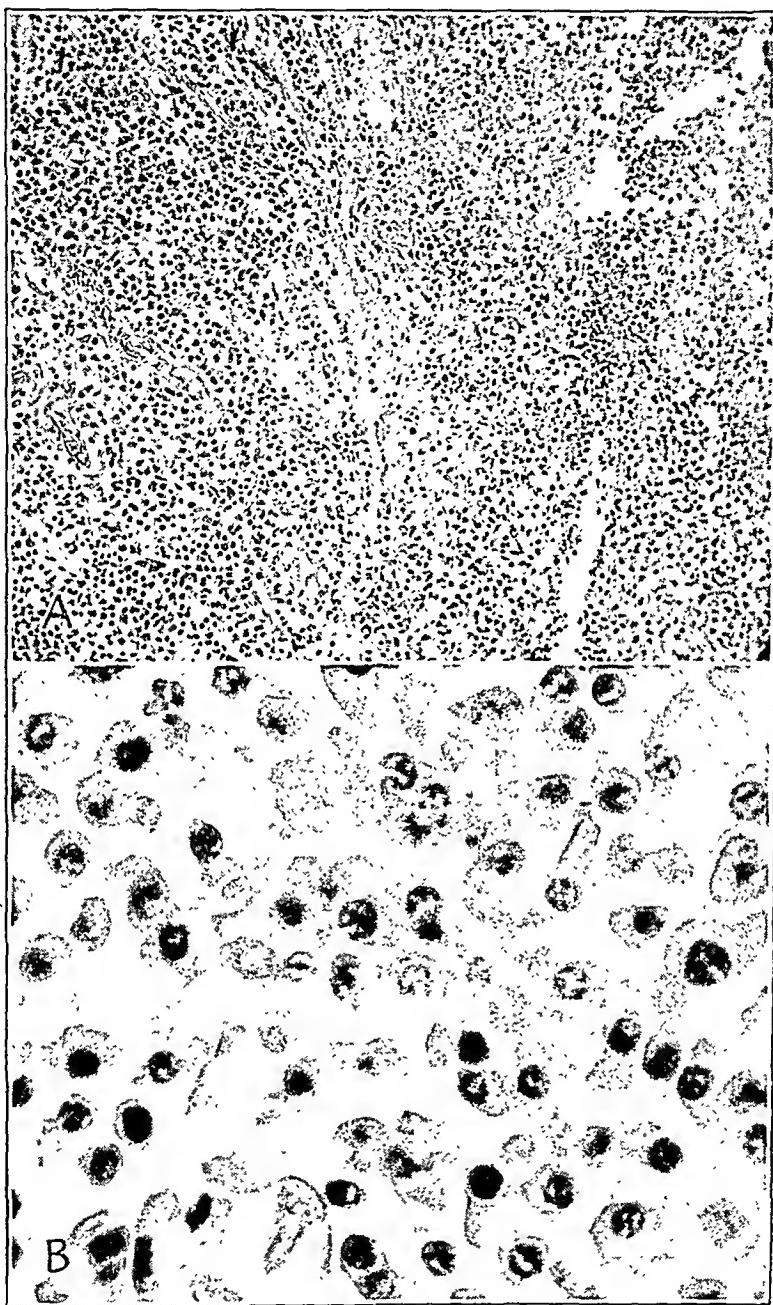
Fig. 5.—Area at margin of a necrotic zone infiltrated with plasma cells and other mononuclears (patient 23 in table 2). *A*, × 105. *B*, × 385.

within the pyramid, and no glomeruli were included. The inflammatory reaction at the junction of necrotic and surrounding tissue was of particular note. In some places not a single inflammatory cell could

be seen in the intercellular spaces (fig. 4 B). Apparently the toxic action of the bacteria was lysing tissue unopposed by any protective action on the part of the body. In other areas neutrophils, eosinophils, plasma cells and lymphocytes formed an inflammatory zone of variable thickness. The plasma cells were numerically greater than or equal to the other inflammatory cells in about half the kidneys (fig. 5), though this varied greatly, even in the same pyramid. They usually formed a secondary line of defense just back of the line of scrimmage between the necrotizing process and the viable tissue. The dearth of neutrophils was especially noticeable (fig. 5) for such an acute necrotizing lesion. The collecting tubules near the necrotic zone often contained polymorphonuclear leukocytes and bacteria, but usually a majority were

Fig. 6.—Hyaline thrombus in a small vessel near the margin of a necrotic zone (patient 21 in table 2); × 110.

free of exudate. Thrombosis of capillaries, usually hyaline, was seen within a narrow zone of the intact parenchyma in a few kidneys (fig. 6). In 5 kidneys extensive thrombophlebitis of the venous system was noted.

In the ascending type of infection the organisms evidently spread to the cortex via the tubules, many of which were seen to be filled with bacteria, neutrophils and necrotic debris. In 8 of the group this was the only infectious process in the cortex. In the more severe lesions (16 cases) localized abscesses had formed, involving many tubules. They were usually 1 to 2 mm. in diameter, few, and adjacent to the bases of the pyramids. In a few lesions the abscesses were 0.5 to 1 cm. in size. In 2 kidneys solitary abscesses were the only change seen in the cortex. Again it was observed that the inflammatory response was

characterized by a relative paucity of neutrophils but many plasma cells. An unusual degree of necrosis was seen in the abscesses with karyolysis, similar to that noted in the papillae, in 3 cases.

The effect of the necrosis of the conduits on the outflow of urine in the nephrons is a problem in itself. In only 9 cases was there any evidence of obstruction causing dilatation such as that seen in the obstructive nephroses due to sulfonamide drugs and hemoglobin. This coincides with the clinical records of a normal urinary output in nearly all cases. Further and more complete investigation of this phase of the disease is needed.

Changes were present in the renal arterial tree without exception. The most noticeable was the intercapillary deposition of hyalin as described in Kimmelstiel-Wilson disease. Mild to moderate hyaline change was seen in 12 of the 26 cases (fig. 7 A). Severe damage was noted in 3, resulting in many hyalinized, functionless glomeruli. Sclerosis of the arteries and arterioles was mild in 17 and severe in 9 (fig. 7 B).

In sections of the pelvis and calices a moderate degree of acute to chronic inflammation was seen. The cellular picture was often similar to that in the interstitial tissue of the kidney. In 3 instances the round cell infiltration without polymorphonuclear cells noted in the pelvis, the cortex and the capsule of the kidney was of sufficient intensity to justify a diagnosis of chronic pyelonephritis, although scars with colloid casts and periglomerular fibrosis as described by Weiss and Parker[16] were not present.

HEALED PAPILLARY NECROSIS

There was one diabetic patient (27 in table 2) in whom the renal papillae had undergone partial to complete necrosis and sloughed away, leaving the base apparently well healed.

The patient, an 81 year old white man, entered the hospital because of exertional dyspnea. He had had frequency of urination for one year but had not known that he had diabetes. On examination the prostate was soft and enlarged to twice the normal size. The blood pressure was 105 mm. of mercury systolic and 60 diastolic. The urine on entry contained no protein and only 3 to 4 pus cells per high power field. The electrocardiogram revealed low voltage and delayed auriculoventricular conduction. Following a fall, an ulcer developed on the ankle, which became infected. He then began to vomit. After several weeks albuminuria (albumin, 4 plus) and severe pyuria were observed. General edema developed. The serum albumin was 3.2 Gm. and the nonprotein nitrogen was constantly between 43 and 52 mg. per hundred cubic centimeters of blood. He died three and a half months after entry.

The cause of death was attributed to acute pulmonary edema due to hypoproteinemia caused by proteinuria and poor food intake. The

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16. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

papillary necrosis of the kidneys apparently did not contribute to the cause of death. Grossly the process was unilateral and partial. On microscopic examination the absent portions of the papillae comprised

Fig. 7.—*A*, intercapillary glomerulosclerosis of moderate severity (patient 21 in table 2); × 250. *B*, severe sclerosis of larger interlobar branch of renal artery (patient 20 in table 2); × 90.

less than one half of the total. Many of the remaining collecting tubules were hyalinized and functionless, although connective tissue proliferation was slight. Some fibrin, a few polymorphonuclear leukocytes and

mononuclear cells were noted between the tubules. No inflammatory changes were visible in the cortex. Some of the papillae were unaffected.

PAPILLARY NECROSIS DUE TO GRANULOMAS IN DIABETIC PATIENTS

Of particular interest were 2 diabetic patients in whom typical necrotizing lesions were apparently granulomatous in origin.

In the case of 1 of these (28 in table 2) with unilateral involvement the microscopic picture was difficult to interpret. The necrotic areas were similar to the others except for the fact that throughout they were more basophilic and at
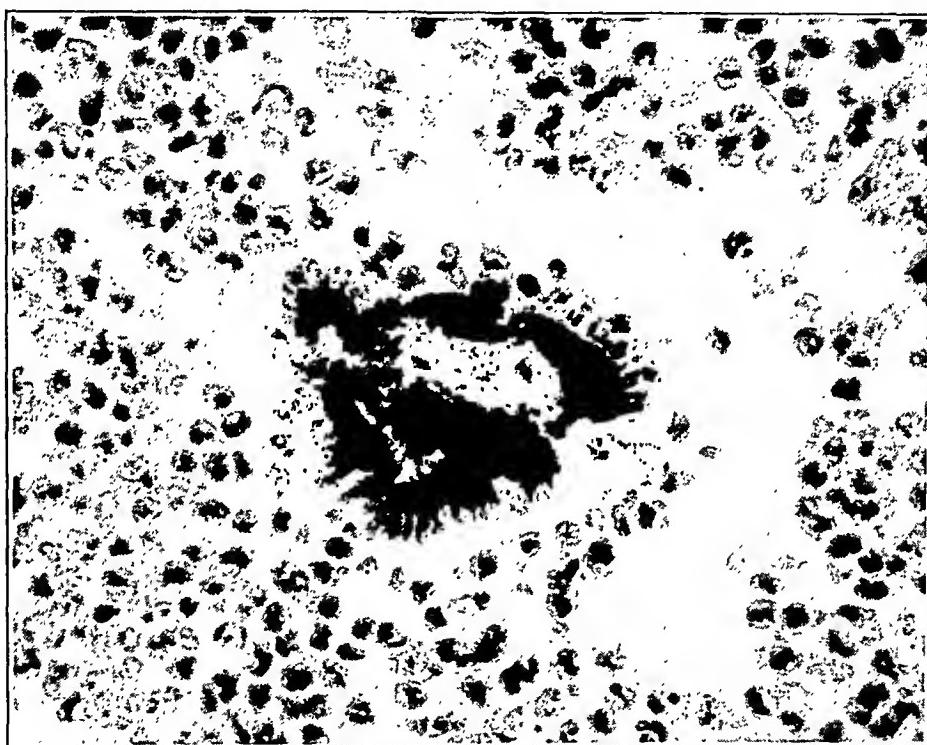
No. 8.—Sulfur granule of actinomycosis (patient 29 in table 2); × 350.

their margins there were occasional epithelioid cells. Smaller but more characteristic tubercles were noted in other parts of the pyramid; none were seen in the cortex. In a section prepared with the Gram-Weigert stain occasional gram-positive cocci were seen in the tubules. Acid-fast organisms were not observed, however, in a prolonged search. Since miliary tubercles were present in the spleen, a diagnosis of tuberculosis combined with pyogenic invasion seemed tenable. There was nothing distinctive in the patient's clinical history. Apparently the course was similar to that of other patients in whom the disease was caused by pyogenic organisms only.

The second patient (29 in table 2) was a 59 year old woman who entered the hospital with a history of pain in the right upper quadrant of the abdomen, cough and vomiting of two months' duration. There had been a 50 pound (22.5 Kg.) loss of weight in two years. On physical examination a mass was found in the right

upper region of the abdomen, which was considered to be the right kidney. The urine contained pus (4 plus), sugar and acetone. Antemortem culture of the urine from the right kidney was negative for acid-fast organisms. Retrograde pyelography gave a normal left ureteropyelogram. On the right the minor calices, particularly the upper, appeared distorted and irregular. After right nephrectomy the patient's illness continued to follow a stormy course. A draining sinus developed in the operative wound. Pus appeared in the urine of the left kidney, the nonprotein nitrogen rose to 109 mg. per hundred cubic centimeters of blood and the patient died within two months in uremia. There was nothing in the clinical history that suggested a gramulomatous lesion.

Microscopic examination of the kidney removed at necropsy showed large areas of shadow-like necrosis which had at their margins in the bases of the pyramids and along the renal columns typical pus-filled cavities containing many of the organized filaments (sulfur granules) of actinomycosis (fig. 8). In the inflammatory exudate polymorphonuclear leukocytes were in great numerical predominance. The available sections of the kidney removed in surgical intervention were made by the frozen method, and the contents of the cavities had fallen out; so no organisms were seen. The histologic picture was that of a granuloma. The papillae were not necrotic. No other lesions of actinomycosis were observed in the body.

ACUTE PYELONEPHRITIS WITHOUT PAPILLARY NECROSIS IN DIABETIC PATIENTS

In this group there were 78 patients, 9 per cent of the patients with diabetes. In 28, or 35.8 per cent, of them the pyelonephritis was due to infection arising elsewhere than in the urinary tract. In 9, no cause

TABLE 3.—*Analysis of Clinical Factors in the Twenty-Nine Patients*

Sex	65% females
Age	79% over 50
Cause of entry	Urinary symptoms.... 20.5%⎫ 41% Uremia............... 20.5%⎭ Diabetic acidosis....... 17% Cutaneous infections.. 14% (31% if those in whom severe cutaneous infections developed on ward are included) Miscellaneous......... 28%
Hypertension	24%
Duration of hospitalization before death	62% less than 15 days 38% over 1 month (1 to 10 months)

of the acute pyelonephritis was apparent in the lower urinary tract, nor was a focus of infection noted elsewhere. In the remainder the pyelonephritis was a complication of infection and/or obstruction of the urinary tract. There were 38 women and 40 men.

In a comparison of these patients and diabetic patients having papillary necrosis there are some data of interest. There was little difference in average age incidence. There were 6 patients, however, under the age of 40 with uncomplicated pyelonephritis, contrasted with only 1 patient under the age of 40 with papillary necrosis. There was

a higher percentage of women with the necrotizing lesion (65 per cent, compared with 49 per cent who had pyelonephritis alone). Obstructive lesions of the urinary tract were more common in the group with pyelonephritis alone (occurring in 26 per cent, compared with 14 per cent of the group with papillary necrosis). Fewer of this group had coma before the apparent onset of the acute disease of the kidney or died in coma as a complication of the latter.

Grossly the kidneys were similar to those of nondiabetic patients with suppurative renal disease. A few had solitary abscesses and perinephric abscesses. On histologic examination this group on the average differed from those with papillary necrosis in that cortical abscesses were more common, neutrophils were more prevalent, and the extent of necrosis
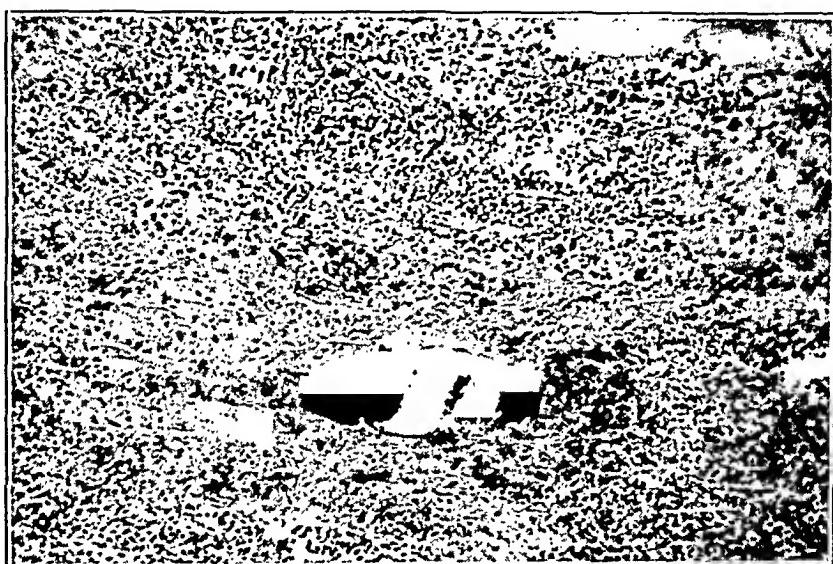
No. 9.—Early necrosis of a solitary collecting tubule in beginning pyelonephritis; × 150.

was not so much out of proportion as compared with the total inflamed area. In this group there was every gradation in the necrotic process from pus-filled abscesses mainly in the cortex to diffuse multiple necrotizing lesions (8 cases) in both the cortex and the pyramids, differing from papillary necrosis only in that the necrotic areas in the papilla were small (fig. 7 A) and involved only a minor portion of the total papilla and pyramid. Thrombosis of veins such as that seen by Harrison and Bailey [15] was noted in 4 cases. Other differences included a smaller number with Kimmelstiel-Wilson lesions (18.5 per cent) and less severe sclerosis of the arterial system. An attempt was made to compare the proportion of the various cells of the renal exudate with that in the group with papillary necrosis. The predominating cells were either neutrophils or lymphocytes, but abundance of plasma cells

was a fairly constant finding. The latter were never so outstanding as in some instances of papillary necrosis, in which the plasma cells constituted the major portion of the cellular exudate (fig. 5). Obviously this comparison was a difficult one to make because of the lack of a good measuring stick, but we feel that the foregoing opinion is justified.

PAPILLARY NECROSIS IN NONDIABETIC PATIENTS

Among the 31,141 nondiabetic subjects there were 1,023 with a diagnosis of pyelonephritis or pyonephrosis. Of these, 21 had either bilateral or unilateral necrosis of the papillae. Table 4 gives the essential data. It is seen that prostatic lesions are the most important cause

TABLE 4.—*Papillary Necrosis in Nondiabetic Patients*

Patient	Primary Disease	Gross Pathologic Condition of Urinary Tract	Age	Sex	Papillary Necrosis
1	Benign hypertrophy of prostate	Infected obstructive uropathy	65	M	Bilateral ?
2	Benign hypertrophy of prostate	Infected obstructive uropathy	87	M	Bilateral
3	Benign hypertrophy of prostate	Infected obstructive uropathy	77	M	Unilateral
4	Benign hypertrophy of prostate	Infected obstructive uropathy	80	M	Unilateral
5	Benign hypertrophy of prostate	Infected obstructive uropathy	78	M	Unilateral
6	Benign hypertrophy of prostate	Infected obstructive uropathy	80	M	?
7	Benign hypertrophy of prostate	Infected obstructive uropathy	80	M	?
8	Carcinoma of prostate	Infected obstructive uropathy	62	M	Unilateral
9	Carcinoma of prostate with postoperative stricture	Infected obstructive uropathy	55	M	?
10	Carcinoma of prostate	Infected obstructive uropathy	74	M	Unilateral
11	Carcinoma of prostate	Infected obstructive uropathy	74	M	Bilateral
12	Carcinoma of bladder	Unilateral pyonephrosis	65	M	Unilateral
13	Carcinoma of bladder	Bilateral pyonephrosis	53	M	Unilateral
14	Carcinoma of cervix	Bilateral pyonephrosis	61	F	Bilateral
15	Carcinoma of cervix	Unilateral pyonephrosis	30	F	Unilateral
16	Urethral stricture	Necrotizing obstructive uropathy	45	M	Bilateral ?
17	Urethral stricture	Bilateral pyonephrosis	44	M	Bilateral
18	Bilateral renal calculi	Bilateral pyelonephritis	58	M	Unilateral
19	Postvaccinal paraplegia with "cord bladder"	Infected obstructive uropathy	11	F	Bilateral
20	Hypertensive heart disease with congestive failure	Only peculiar appearance of pyramids noticed grossly	51	M	Bilateral ?
21	Adenocarcinoma of ovary with spread to bladder	Bilateral pyelonephritis with abscesses in left kidney	33	F	Unilateral ?

in the nondiabetic patients. In 20 of the 21 there was chronic obstruction of the urinary tract. The incidence of necrosis in this group has definitely decreased in recent years, presumably owing to better control of infections of the urinary tract with sulfonamide drugs and penicillin.

Pathologic Observations.—The gross necrotic lesions were rarely described by the autopsy surgeon. They were probably overlooked because of the overshadowing effect of the primary disease of the urinary tract, in contradistinction to the lesions of the papillae in diabetic patients, which usually stand alone as gross pillars of pathologic change. The histologic picture differed from that of the diabetic group in that the lesion was usually smaller and more often confined to the tip of the papilla or was present only in its central portion. Plasma cells were rarely outstanding in the cellular exudate. Again, as in the diabetic

group, all gradations were seen between microscopic abscesses in the papillae and extensive necrosis. Thrombosis of renal vessels did not appear to be a factor.

Clinical Findings.—A review of the clinical records of these patients gave no clues to how an antemortem diagnosis could be made. As Günther [1] pointed out, the primary disease plus infection usually completely masks the necrosis in the kidneys.

COMMENT

The major clinical problems connected with papillary necrosis concern diagnostic criteria, differential diagnosis and treatment. No clinical diagnosis of Günther's necrosis that was substantiated by autopsy was made until after this study was begun. The condition has now been diagnosed ante mortem in several patients. We do not believe that rigid diagnostic criteria can be laid down for all cases. However, the lesion should be considered in any investigation of the following types of diabetic patients: (1) those with sepsis in whom urinary symptoms or findings suddenly develop, (2) those who go into coma rapidly with nitrogen retention but without an antecedent history of pyelonephritis, (3) those with low grade pyelonephritis who suddenly become worse, (4) those with hematuria or renal colic, (5) those with severe diabetic acidosis whose blood sugar and carbon dioxide–combining power may return to normal after treatment but who show an increasing degree of stupor and rising nonprotein nitrogen when shock and tubular damage can be excluded, and (6) those with characteristic roentgenographic changes.

In many cases the pyelograms are diagnostic, particularly if the lesions are bilateral and symmetric. All gradations of involvement of the papillae may occur; hence the appearance of the calices on roentgenograms depends on the degree of necrosis. Günther [1] and Alken [11] emphasized the following roentgenographic changes: (1) The earliest lesion is a deformity of the tip of the calix such as that seen in pyelonephritis; (2) with narrowing of the neck of the calix by separated particles, a picture of peripheral excavation extending into the cortex may occur; (3) ring shadows may be seen in the necrotic papillae; (4) replacement of the concave tip of the calix by dilation so great as to suggest cavern formation; (5) tips of whole papillae may slough off and appear as free masses in the renal pelvis.

In the differential diagnosis the diseases to be considered are: (1) pyelonephritis without necrosis, (2) stone with renal colic, (3) renal tuberculosis and (4) renal tumor. When pyelonephritis is present without necrosis, the patient is rarely as ill and the course is less fulminating than when necrosis is present. Pyelograms may be diagnostic in some cases but will not be so in all, since the differences between the

two groups are not always marked or striking. Stone with symptoms of renal colic may be confused with Günther's necrosis when colic is caused by sloughing-off of a necrotic papillary tip and resulting ureteral blockage. The pyelogram may or may not be helpful hère, for stones and sloughed tissue may be roentgenographically similar. The diabetic state and the course of the disease may favor the diagnosis of the necrotic lesion. In some cases surgical intervention alone may establish the diagnosis (illustrated in the case of Mellgren and Redell[12]). We have had no patients who presented renal colic. We are aware of a patient of a confrere, whose renal necrosis was diagnosed by roentgenograms and study of the kidney and who was treated by surgical removal of the kidney, whose presenting symptom was severe renal colic. This patient is alive after one year.

In diabetic patients with hematuria, all the usual causes should be excluded. With renal tuberculosis or tumor this may be difficult, for the pyelographic outline may be similar to that seen in necrosis. However, in most diabetic patients both kidneys and all of the papillae become involved, which should be diagnostic. In unilateral disease differential points are few or absent. Recently we have observed an elderly diabetic patient who died four days after she first entered the hospital with symptoms of high fever, cardiovascular disturbances, pyuria and hematuria, who was too ill for pyelograms to be made. We diagnosed papilary necrosis, but a hypernephroma was found at necropsy.

In a consideration of the cause or causes of this unusual necrotizing lesion, several factors may be considered. First, as Günther[1] and others have emphasized, is the anatomic fact that the papillae and the pyramids have a poor blood supply as compared with the rest of the kidney. All of the blood except a small amount from branches of the arteries that directly supply the renal pelvis reaches the peritubular capillaries after it has gone through the glomeruli. In addition we would emphasize the physiologic fact that the blood has now lost 10 per cent of its water, much of its sugar, chlorides and nitrogenous products while retaining its protein, and thus its osmotic pressure is increased. Whether or not this may have an effect on the migration of leukocytes is not known, but presumably such blood, being more viscid, tends to undergo intravascular clotting more readily. The fact that the necrosis is anatomically limited to the pyramids is in itself strong evidence of the importance of the blood supply. At least no other explanation for its abrupt limitation at the arcuate vessels and the papillary-calicine angle comes to mind. Contributing further to the lack of blood flow are the sclerotic changes in the arterial system. These were present in all kidneys. The arterial and arteriolar changes were mild to moderate in 17, while in the remainder the changes were severe. Intercapillary glomerulosclerosis, seen in 60 per cent, would further tend to embarrass

the pyramidal blood flow.   In patients with severe Kimmelstiel-Wilson disease, in whom loss of protein was sufficient to produce hypoproteinemia, the effect on immune processes, especially the possible decrease of gamma globulin, is one to be considered and one well worth further investigation.

Second, and possibly more important, is the diabetic state, especially if acidosis is present.   Menkin's [17] work on inflammation indicates that in the early stages of the inflammatory process the fluid exudate is alkaline and therefore favorable to the preservation and the function of polymorphonuclear leukocytes.   Later, with death of tissue, acid bodies accumulate locally, and as the p_H falls below 6.9 the neutrophils disappear and mononuclears become numerically predominant.   Menkin showed that in diabetes acid bodies were formed more rapidly and thus influenced the course of the inflammatory process by causing a more rapid disappearance of polymorphonuclear cells.   It seemed to us that the pattern of the cellular exudate in diabetic patients was different from that in nondiabetic patients.   Especially in papillary necrosis the exudate was poor in polymorphonuclears.   Furthermore, in diabetic acidosis with papillary necrosis, once the basement membrane is necrotic, the effect of a bacteria-laden, highly acid, sugar-filled urine escaping into the intercellular tissues is to be considered.   This may effect change in the inflammatory reaction of the tissues in the precise manner already noted; i. e., an exudate small in amount and poor in neutrophils and fibrin accumulates, resulting in an apparent inability to wall off the infection. In obstructive lesions of the urinary tract urine may escape into the tissues through necrotic walls.   If there is a normally functioning lower urinary tract, the pressure differential between intercellular fluid and intratubular flow should not be great enough to cause the same phenomenon unless some of the individual tubules are blocked by exudate. Thus the effect may be compared with that seen in urinary extravasation around the urethra, where necrosis of tissue followed by gangrene is common.

The relation of glycosuria to the development of both pyelonephritis and the necrotizing lesion is a problem in itself.   An attempt was made to reproduce the lesion in depancreatized rats by prolonged glycosuria and ureteral obstruction (ureters tied with silk).   Pyonephrosis developed in all these rats, although depancreatized rats are relatively resistant to infection, whereas only hydronephrosis developed in the nondiabetic rats similarly treated.   In none of the rats of either group, however, did the classic Günther's lesion develop.   This may have been

17. Menkin, V.: Diabetes and Inflammation, Science 93:456, 1941; On Mechanism of Enhanced Diabetes with Inflammation, Am. J. Physiol. 134:517, 1941; Biochemical Factors in Inflammation and Diabetes Mellitus, Arch. Path. 34:182 (July) 1942.

due to the fact that atrophy was extreme, and by the time the rats died only a shell of pyonephrotic kidney was left. The relationship of hyperglycemia to infection in general and of glycosuria to renal infection in diabetes still remains an unsolved problem despite much experimental work on the subject. The fact that papillary necrosis has been produced by administration of vinylamine[18] and tetrahydroquinone[19] may have some significance in that it indicates the papillae are the parts of the kidney most susceptible to injury by these agents.

A third factor to be considered is the type and the virulence of the bacteria. Early in our studies we assumed that E. coli was the chief offender, but as bacteriologic data accumulated, our attention turned to Staph. aureus. The masses of blue-staining organisms seen in sections of the kidney stained with hematoxylin and eosin are probably staphylococci. In those patients with foci of infection elsewhere, as manifested in carbuncles and cellulitis, on whom no bacteriologic study was made at necropsy we assume that Staph. aureus was the cause of the renal necrosis. In those cases without a distant focus it seems probable that an ascending staphylococcic infection was present. The poor resistance of diabetic patients to Staph. aureus is well known, as carbuncles, cellulitis and infected feet are common complications. The coagulase enzyme (destroying fibrin) of the staphylococcus plus the necrosin factor discovered by Menkin[20] (a euglobulin found in inflammatory exudates, capable of causing necrosis), operating together, help to account for the extensive necrosis seen. Günther[1] noted the presence of E. coli and staphylococci in many of his cases and believed that they were the primary causes of the disease. Baldwin and Root[21] stressed the serious nature of renal infections in the diabetic patient, particularly those of hematogenous origin caused by hemolytic Staph. aureus.

The presence of tuberculosis of an unusual character, apparently combined with a minor degree of pyogenic infection, resulting in papillary necrosis, as it did in one instance in our series, must be extremely rare. Papillary necrosis due to actinomycosis of the kidney is likewise most unusual. The localization of the actinomycotic process in the pyramid in such a way as to produce necrosis of the papilla without directly involving it is difficult to explain. Stoudensky[4] noted both actino-

18. Levaditi, C.: Recherches expérimentales sur la nécrose de la papille rénale, Arch. internat. de pharmacodyn. et de thérap. 8:45, 1901.

19. Rehns, J.: D'une nécrose typique de la papille rénale determinée par la tétrahydroquinoléine et certains de ses dérivés, Arch. internat. de pharmacodyn. et de thérap. 8:199, 1901.

20. Menkin, V.: Chemical Basis of Injury in Inflammation, Arch. Path. 36:269 (Sept.) 1943.

21. Baldwin, A. D., and Root, H. F.: Infections of the Upper Urinary Tract in the Diabetic Patient, New England J. Med. 223:244, 1940.

mycosis and tuberculosis associated with the disease, but neither caused the papillary lesions.

Other considerations include the known fact that antibody response is poor in many diabetic persons.

No explanation has been presented so far as we know for the excessive plasma cell infiltration evidenced in the inflammatory exudate. This is not a pathognomonic sign, for occasionally similar numbers are seen in nondiabetic patients with pyelonephritis. Mellgren and Redell [12] mentioned plasma cells in their report of papillary necrosis occurring in 2 nondiabetic patients. But if the average over-all histologic picture is taken, the difference in cellular exudates is unquestionable.

The role of the peritubular hyaline substance called para-amyloid by Mellgren and Redell [12] is difficult to evaluate. In our experience an increase of hyaline material around the tubules in the papillae and the medulla is not uncommon in the older age groups. We did not see any increased incidence in the diabetic group.

The spreading type of necrosis observed in the papillae and pyramids, associated with many bacteria and little inflammatory reaction, is really a gangrenous process in the true sense of the word. The formation of a line of demarcation in the pyramid, sloughing of the affected part and finally occasional healing of the pyramidal remnant are further characteristics of gangrene. It differs from gangrene ordinarily seen elsewhere in its precise limitation to multiple small areas. Gangrene as a complication of diabetes is too well known for comment, whether it occurs in the extremities, the skin, the lungs or elsewhere.

The fact that papillary necrosis may occur in diabetic patients without obstruction of the urinary tract, while on the contrary it is practically limited to patients with urinary obstruction in the nondiabetic group, emphasizes the importance of infection in the diabetic group. Of the 107 patients with diabetes, 33.6 per cent had sepsis resulting in secondary renal infection. Better and earlier use of the new chemotherapeutic agents should be helpful in preventing many of these lesions.

The predilection of papillary necrosis for diabetic persons beyond the age of 40 (the condition developed in only 1 of 9 under 40) may be due in part to the severity of vascular lesions occurring beyond that age. No conceivable explanation can be given for the apparently greater incidence of necrosis in women.

Prevention, as already noted, is the most important part of treatment. The use of penicillin and sulfonamide compounds for the staphylococcic infections and possibly in the future the use of streptomycin for E. coli infections may save some of these patients. We have in our series a patient whose lesions healed and know of another (case to be reported). In none of the cases summarized in this article can it be considered that the patient received adequate chemotherapy. In some patients

death occurred too soon after they entered the hospital, and the gangrenous process was too overwhelming by the time the patient was seen, for any form of therapy to be of value. It is essential that urologists realize that the lesions are usually bilateral in those diabetic patients who are without unilateral obstruction, as removal of one kidney with necrosis may speed a latent or an early process in the opposite kidney. In the nondiabetic group the important objective is the treatment of all obstructive lesions.

SUMMARY AND CONCLUSIONS

Acute necrosis of the renal papillae was observed in 29 of 859 diabetic subjects in a series of 32,000 necropsies. Papillary necrosis is more common in women and is exceedingly rare in patients under 40 years of age as contrasted with pyelonephritis without necrosis in diabetic patients, among whom men predominate and occurrence under 40 is not unusual. The disease is highly fatal; only once was healing observed. It is most often part of acute pyelonephritis, which may be secondary to ascending infection of the urinary tract or to pyogenic foci elsewhere in the diabetic subject. E. coli and Staph. aureus are the organisms most frequently isolated from acute pyelonephritis. The latter disease may be secondary to sepsis, which is an important cause of pyelonephritis in diabetic patients. Tuberculosis and actinomycosis were each noted once as the cause of papillary necrosis. The diabetic state, renal vascular disease (including Kimmelstiel-Wilson disease) and poor blood supply of the papillae are apparently contributing factors in the pathogenesis.

In the same necropsy series, papillary necrosis was noted in 21 of 1,023 patients with pyelonephritis who were not diabetic; in 20 it occurred as a complication of urinary obstruction, which was most often due to disease of the prostate gland.

Criteria for the diagnosis of papillary necrosis in diabetic patients cannot be rigidly defined but should include hematuria, renal colic, unexplained coma and sudden increase in severity of symptoms of known pyelonephritis. Retrograde pyelograms are usually diagnostic. Treatment should be directed toward preventing infection by early use of chemotherapy. After the onset of pyelonephritis, specific chemotherapeutic agents should be used in adequate amounts, as some patients may be saved.

EOSINOPHILIC GRANULOMA OF BONE

Report of a Case with Multiple Lesions of Bone and Pulmonary·Infiltration

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DURING the past years, approximately 30 cases of eosinophilic granuloma of bone have been reported in the medical literature. Since it has been noted that this condition is confined to the skeleton, often involving only a single bone, it has also been called "solitary granuloma of bone."[1] The case herein reported has been ·under observation for almost three years since the diagnosis was established and is considered noteworthy because of the presence of multiple skeletal lesions and a coexistent pulmonary infiltration. The latter may well be an instance of visceral involvement.

REPORT OF A CASE

The patient was a 31 year old lawyer who was admitted to the Medical ·Service of Vanderbilt University Hospital on Jan. 6, 1943, complaining of an intermittent headache in the left occipital region, of·about seven months' duration, and backache in the lower region, which he had first noticed three months before his admission.

The headache had begun insidiously and was never severe. It remained localized in the region of the left side of the occiput and was neither constant nor progressive. Remissions for as long as a week were frequent. Use of salicylates usually afforded prompt relief. The headache was not associated with visual disturbances, weakness, paresthesias, syncopal attacks or convulsive seizures.

The only other complaint was that of intermittent ache low in the back, which he referred to the region of the left sacroiliac joint. This pain was aggravated by sudden movement. There had been no apparent limitation of motion and no radiation of the pain into the lower extremity. There was no significant history of trauma. He had been troubled for the past few months by a nonproductive cough. There had been no pains in the chest.

Physical Examination.—At the time of admission, it was noted that he was a robust· young man who did not seem ill. His temperature was 98.6 F., pulse rate 110, respiratory rate 22 and blood pressure 122 mm. of mercury systolic

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1. Otani, S., and Ehrlich, J. C.: Solitary Granuloma of Bone Simulating · Primary Neoplasm, Am. J. Path. **16**:479-490 (July) 1940.

and 88 diastolic. Tenderness was observed on deep palpation over an area of 1 to 2 cm. in diameter in the left parietal region of the skull. There was no palpable bony defect or tumor at this site. No intracranial bruit was heard.
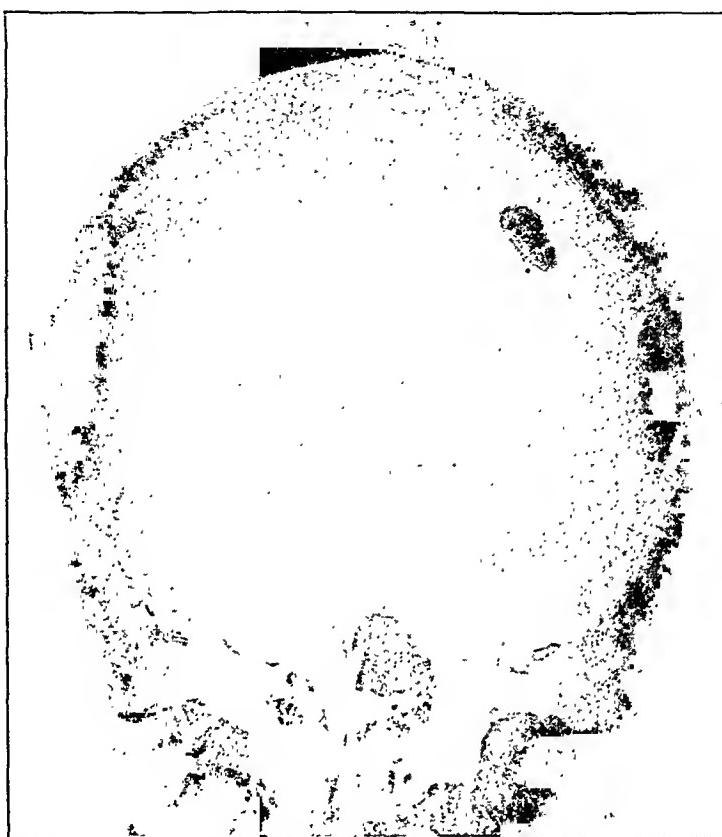
Fig. 1.—Roentgenogram of the skull, December 1942, showing defects in the left parietal and the occipital bone.
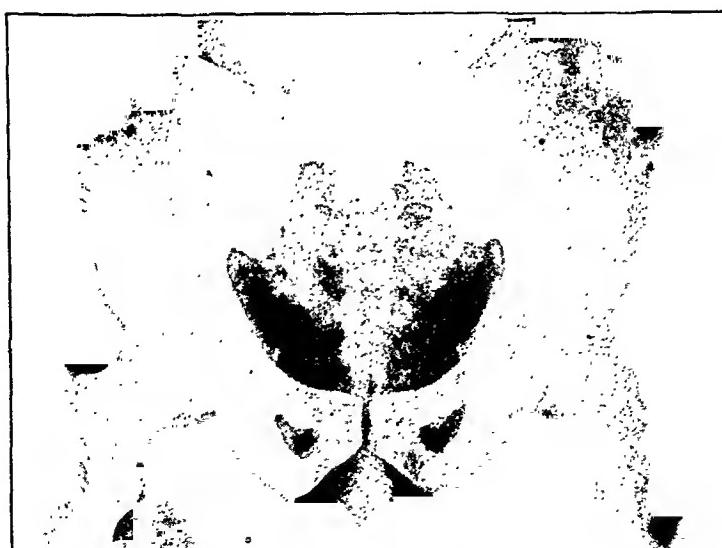
Fig. 2.—Roentgenogram of the pelvis, April 1943, showing destructive area in the left iliac wing and the pubic bones. Gas shadows are present over the right ilium.

Fig. 3.—Roentgenogram taken in March 1943, showing destructive lesion in the third lumbar vertebra.
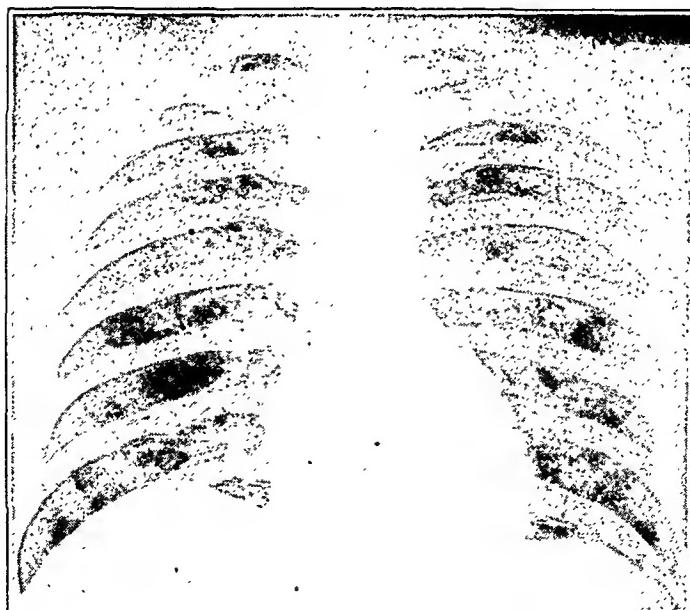
Fig. 4.—Roentgenogram of the chest, March 1943, showing nodular infiltration of the upper fields of both lungs.

The ocular fundi were normal. The thyroid was not enlarged, and there was no enlargement of peripheral lymph nodes. The heart and abdomen were not remarkable. The examination of the lungs revealed no dulness, alteration in breath sounds or rales. There was no demonstrable enlargement of the liver or spleen. Examination of the spine revealed no localized deformity or tenderness, and
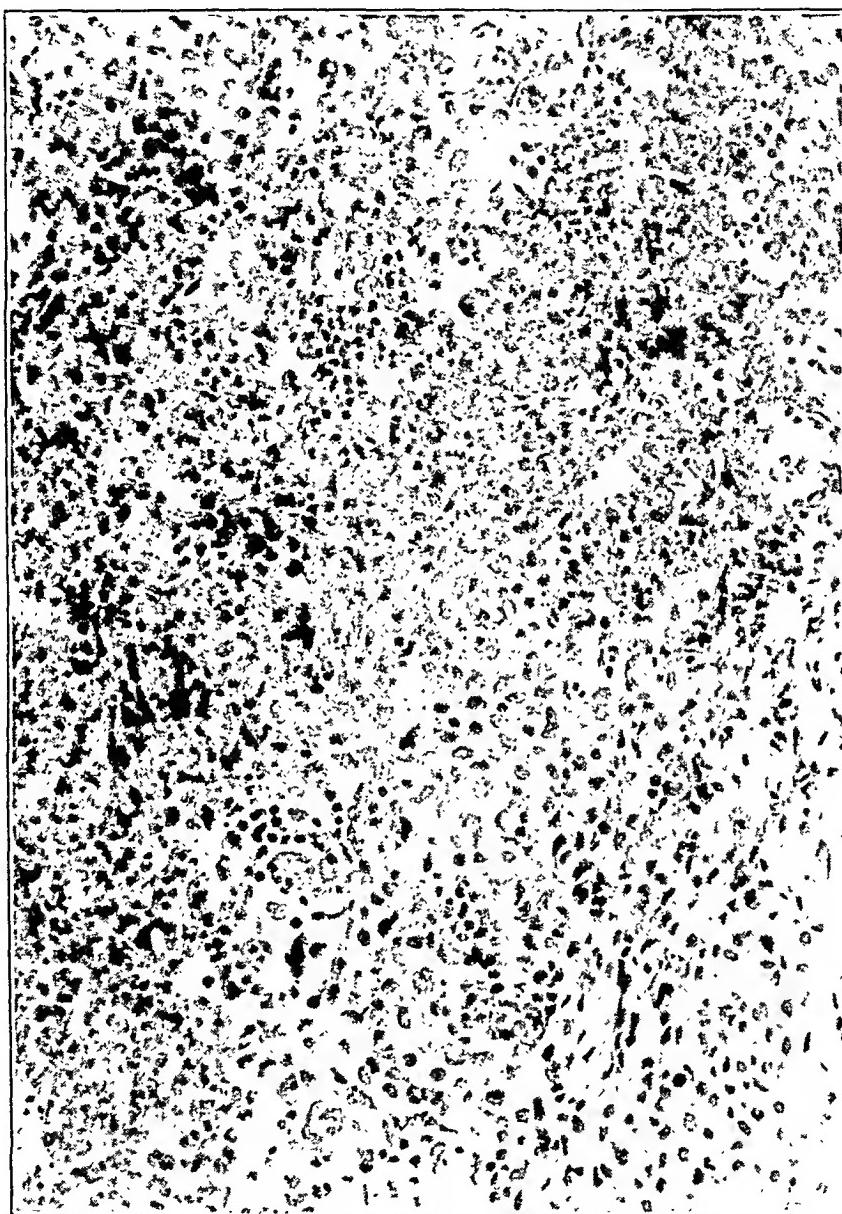
Fig. 5.—Photomicrograph of tumor tissue, showing the large collection of eosinophils and histiocytes.

moblity was unimpaired. The prostate was normal in consistency and size. The cranial nerves were intact. There were no changes in the motor or sensory nerves. The reflexes were physiologic.

Laboratory Studies.—The spinal fluid, which was under normal pressure, contained 3 cells and 36 mg. of protein per hundred cubic centimeters. Wassermann tests of the spinal fluid and the blood elicited negative reactions. The acid

phosphatase content was 1.8 and the alkaline phosphatase content 6.6 Bodansky units.

The nonprotein nitrogen content was 37 mg. per hundred cubic centimeters, and the total serum protein content was 5.4 Gm. per hundred cubic centimeters, with an albumin fraction of 3.1 Gm. There was mild leukocytosis, and a 5 per cent eosinophilia was found on all occasions. The serum calcium content was 10.4 mg., the inorganic phosphorus content 4.4 mg. and the cholesterol content 263 mg. per hundred cubic centimeters. The urine was normal at all times, and Bence-Jones protein was never found. The vital capacity was 4,800 cc., and the electrocardiogram was normal.

Roentgenologic Studies.—Roentgenograms of the skull (fig. 1) revealed two bony defects, one in the left parietal bone, just above the occipitoparietal suture and the other in the occipital bone, near the site of the torcular Herophili. Small
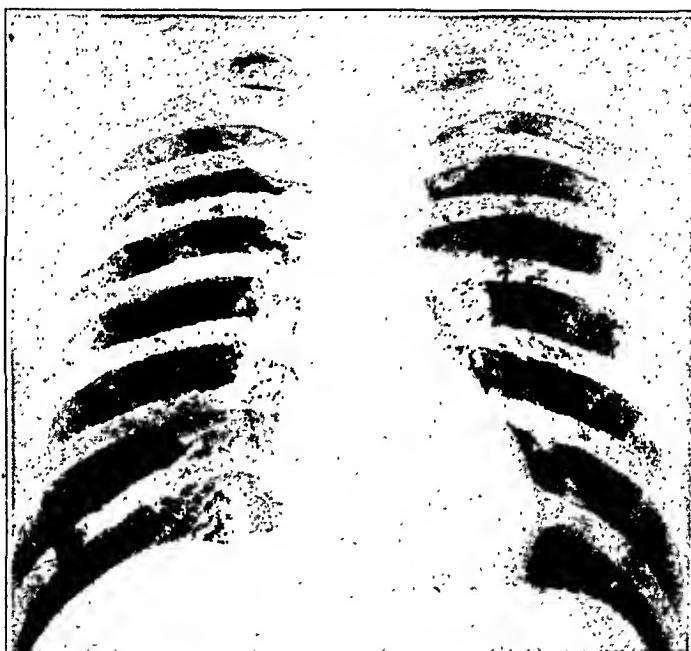
Fig. 6.—Roentgenogram of the chest, April 1945, showing striking decrease in infiltration of the lung.

areas of destruction were found in the left ilium and pubis (fig. 2). An early lesion in the body of the third lumbar vertebra was detected elsewhere in February 1943. A subsequent examination in March 1943 at Vanderbilt University Hospital revealed the fully established defect (fig. 3). No pathologic change was noted in roentgenograms of the long bones, hands and feet. A roentgenogram of the chest (fig. 4) revealed a fine nodular type of infiltration in the upper halves of both fields of the lungs.

Diagnosis.—The general well-being of this patient, the multiple skeletal lesions and the apparent absence of any primary malignant focus made a diagnosis of metastatic malignant growth unlikely. There was no Bence-Jones proteinuria to support a diagnosis of multiple myeloma. A clinical diagnosis of eosinophilic granuloma of bone was ventured, and it was thought that the pulmonary pattern did not conform to any well known disease, nor did it suggest any unusual con-

dition such as sarcoid, histoplasmosis or Loeffler's syndrome. This patient's mild but persistent eosinophilia, although not a constant finding in other reported cases, was also consistent with a diagnosis of eosinophilic granuloma of bone.

Biopsy.—On Feb. 6, 1943, the lesion in the left parietal region was explored (Dr. Walter Dandy) at the Johns Hopkins Hospital. The normal bone in this region had been replaced by tissue of a whitish yellow color having the consistency of cream cheese. This was removed with a curet. It was noted that the dura at the base of the bony defect was not involved.

Microscopic Examination.—The curetted tissue was seen to consist chiefly of histiocytes, large cells with a single irregularly shaped nucleus and a pale pink

Fig. 7.—Roentgenogram taken in December 1943, showing healed lesion in third lumbar vertebra.

cytoplasm (fig. 5). None of these cells contained sufficient fat to be classed as "foam cells" or lipophages. A few were undergoing necrosis. There were many focal accumulations of eosinophils. Small round lymphocytes and plasma cells were scattered diffusely throughout the tissue, save for one or two areas of fairly dense lymphocytic infiltration. There was a decided increase in fibrous connective tissue and some proliferation of the endothelium to form new capillaries.

Treatment and Further Course.—The mild headache and backache and a troublesome nonproductive cough had continued to cause him considerable dis-

comfort. On March 22, 1943, the roentgenologic studies were repeated as a preliminary to radiation therapy. In addition to the lesions noted previously, which had not changed, there was a well outlined area of destruction in the body of the third lumbar vertebra (fig. 3) approximately 1.5 cm. in diameter.

Roentgenologic therapy was started on March 22, and the first series of treatments was completed on April 6. Divided doses of 300 r (with backscatter) were given with 200 kilovolts and 20 milliamperes through 0.5 mm. of copper and 1 mm. of aluminum filtration at a distance of 50 cm. and through suitable-sized portals for each field. The skull was treated through an occipital field angled through the lesions of the occipital and posterior parietal areas on one day. On the second day the anterior portals of the right and left lungs were treated, and on the third day the posterior part of the left ilium to the lower part of the lumbar region of the spine and the anterior fields of the symphysis pubis were treated. This rotation of treatment through the portals was followed until a total of 1,500 r
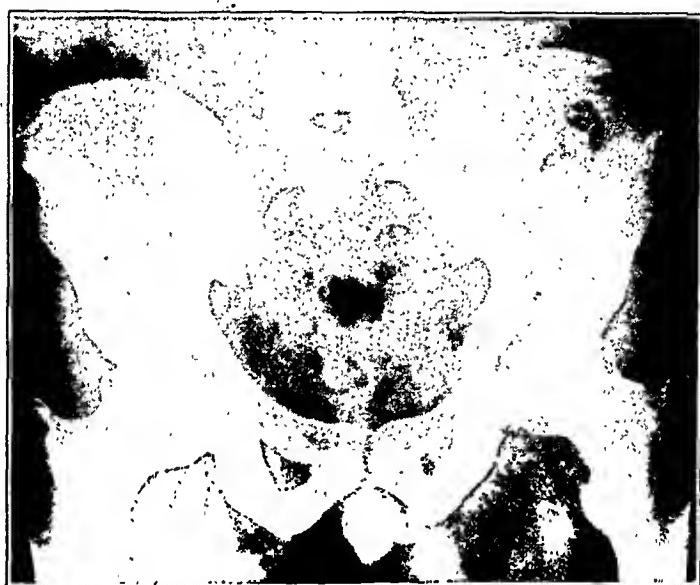
Fig. 8.—Roentgenogram of pelvis, December 1943, showing partial healing of lesions in the left side of the ilium and those around the symphysis pubis. Several gas shadows are present below the lesion in the left side of the ilium. A new lesion is present in the right superior side of the iliac spine.

to each was administered. The posterior fields of the right and left lungs each received 600 r. On July 15, 16 and 17, daily doses of 500 r were given to the left ilium and hip through the anterior, lateral and posterior portals, in rotation. On December 9, 10 and 11, daily doses of 400 r were administered to the left lower molar region. On Oct. 16, 1944, a single dose of 500 r was given to the new lesion in the posterior part of the right ilium.

Although the roentgen ray evidence of resolution of the lesions was not soon apparent, there was prompt relief of the aching pains of which the patient had previously complained. In addition, the cough disappeared.

On June 18, 1943, roentgen ray examination of his skull, spine, chest and pelvis revealed evidence of healing of the lesions in the left ilium, pubis and third lumbar vertebra. The defects in the skull were essentially unchanged. The small nodular infiltrations in the lungs had decreased considerably in size (fig. 6). About

a month later, the lesion in the third lumbar vertebra was almost completely healed, as were the lesions in the pubis (figs. 7 and 8). In December 1943, the patient complained of pain in the left jaw. Roentgen ray examination revealed a small area of destruction in the left mandible. Similar lesions have been reported.[2] On Oct. 16, 1944 there was also a new lesion in the crest of the right ilium. It was noted that the healing process was progressing in the old lesions.

In April 1945, the bony defect at the site of curettage was seen to be essentially unchanged, whereas the other lesion in the skull had almost completely healed. The lesions elsewhere exhibited much improvement. The tardiness of the healing process in the curetted lesion is at variance with the results reported by others.

COMMENT

The benign character of this patient's course has persisted to date. He has maintained his weight and usual vigor and has been actively engaged in the practice of law. There has been no fever, in contrast to several reported cases in which, because of severe pain, local signs of

Tabulation of Data by Mallory [7]

I. Letterer-Siwe's disease	(Reticuloendotheliosis; aleukemic reticulosis; nonlipid histiocytosis) Children under 2 years Fever; skin rash; anemia; purpura; splenomegalia Histologically: proliferation of monocytes and clasmatocytes in bone, skin, lymph nodes and spleen, with or without deposits of lipids
II. Hand-Schüller-Christian syndrome	Older children Defects in cranial bones; exophthalmos; diabetes insipidus Xanthoma deposits with or without eosinophils Associated lymph nodes may show typical eosinophilic granuloma, with or without deposits of cholesterol
III. Eosinophilic granuloma	Children and adults Single or multiple lesions of the bone Good general health; low grade fever; leukocytosis with eosinophilia; local tumor, sometimes painful Histologically: granuloma with eosinophils Cured by local excision, roentgen rays or occasionally spontaneously

inflammation, fever and leukocytosis, it was difficult to rule out Ewing's tumor of bone. This particular situation was notable in the case recently reported by Solomon and Schwartz.[3] There has been no involvement of the long bones with the threat of spontaneous fracture as noted in a report of a case by Versiani and others.[4]

We are unable to state with certainty that the nodular infiltration of the lungs observed on roentgen ray examination is a visceral mani-

2. Bailey, J. W., and Freis, E. D.: Eosinophilic Granuloma of Bone with Manifestations in Jaw, J. Am. Dent. A. **31**:91-94 (Jan.) 1944.

3. Solomon, H. A., and Schwartz, S.: Eosinophilic Granuloma of Bone, J. A. M. A. **128**:729-731 (July 7) 1945.

4. Versiani, O., and Junqueira, M. A.: Hand-Schüller-Christian's Syndrome and "Eosinophilic or Solitary Granuloma of Bone," Am. J. M. Sc. **207**:161-166 (Feb.) 1944.

festation of this disorder, which has hitherto been described as involving only bone, even though irradiation of the pulmonary fields produced a decided improvement in the lungs and was associated with disappearance of cough. However, in consideration of the fundamental similarity of eosinophilic granuloma of bone, Hand-Schüller-Christian disease and Letterer-Siwe's disease (as stressed by Jaffe and Lichtenstein,[5] Green and Farber,[6] Mallory[7] and others), such a possibility does not seem remote (table).

<div align="center">CONCLUSION</div>

A case of eosinophilic granuloma of bone is reported, characterized by multiple skeletal lesions and a coexistent nodular pulmonary infiltration.

The latter is believed to be a visceral (pulmonary) involvement as a part of the general picture of eosinophilic granuloma of bone. If this is true, this is the first such case reported. This fact together with the multiplicity of the lesions of the bones, prompted this publication.

5. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone: Condition Affecting One, Several or Many Bones, but Apparently Limited to Skeleton, and Representing Mildest Clinical Expression of Peculiar Inflammatory Histiocytosis Also Underlying Letterer-Siwe's Disease and Schüller-Christian Disease, Arch. Path. **37**:99-118 (Feb.) 1943.

6. Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, J. Bone & Joint Surg. **24**:499-526 (July) 1942.

7. Mallory, T. B.: Medical Progress. Pathology: Diseases of Bone, New England J. Med. **227**:955-960 (Dec. 10) 1942.

INDUCED MALARIA OF FOREIGN ORIGIN

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IT IS the purpose of this report to describe certain features of induced malaria as observed in the treatment of 243 patients with neurosyphilis. The establishment by the Surgeon General of a center for the treatment of neurosyphilis in a hospital to which numerous patients with naturally acquired malaria had been admitted from overseas provided a unique opportunity to study the transmission of Plasmodium vivax malaria under controlled conditions. It also afforded a means of observing the untreated primary malarial attack with respect to symptoms, complications, course, response to antimalarial therapy and rate of relapse.

MATERIAL AND METHODS

The 243 patients included in this study were suffering from asymptomatic (77 per cent) or symptomatic (23 per cent) neurosyphilis. One hundred and seventy-five of these patients were white and comprised the chief group for study. The remaining 68 patients were Negroes; 45 of these were given quartan malaria, and an effort was made to transmit tertian, or P. vivax, malaria to the other 23 patients. The 243 patients ranged from 19 to 50 years of age, the majority being in the third and fourth decades of life. Careful physical evaluation of each patient revealed no contraindication to malarial therapy.

One group of patients was inoculated by means of laboratory bred Anopheles mosquitoes[1] infected with P. vivax. This group will hereafter be referred to as the group with "mosquito-induced" malaria. . The mosquitoes had been previously infected from patients with relapsing P. vivax malaria, contracted in the Pacific or the Mediterranean area. Another group of patients was infected by intravenous inoculation of blood (usually 7 cc.) containing the trophozoites of the same strains of P. vivax. A third group was infected by inoculation of blood

1. Ehrman, F. C.; Ellis, J. M., and Young, M. D.: Plasmodium Vivax Chesson Strain, Science **101**:377 (April 13) 1945. Young, M. D.; Stubbs, T. H.; Moore, J. A.; Ehrman, F. C.; Hardman, N. F.; Ellis, J. M., and Burgess, R. W.: Studies in Imported Malarias: Ability of Domestic Mosquitoes to Transmit Vivax Malarias of Foreign Origin, J. Nat. Malaria Soc. **4**:127 (June) 1945.

containing a Trinidad strain of Plasmodium malariae producing quartan malaria.[2] The majority of the last group were Negroes.

Blood smears were examined daily for malarial parasites. With the patients who had been bitten by infected mosquitoes the taking of smears was begun six days later. When a positive thick smear was found or when signs or symptoms of malaria developed, the patient was transferred to the malaria ward. With the patients who had been inoculated intravenously with blood, daily examination of smears began the day after inoculation.

The routine care of the patient after admission to the malaria ward can be summarized as follows: In general, he was kept in bed unless he was feeling well enough, when afebrile, to be up and about the ward. Accurate notes were kept with reference to his temperature, his intake and urinary output of fluids, his blood pressure and his weight. Urinalyses were done twice weekly, and complete blood counts and determinations of blood nonprotein nitrogen, at weekly intervals. A general diet was given to the patient if his temperature was below 100 F. If it was above 100 F. and if the patient had the inclination to eat, he was given a diet of soft foods or liquids, high in vitamins and calories. Taking of fruit juices and eggnogs between meals was encouraged. Intravenous infusions of dextrose in saline solution were given liberally, particularly when the patient had been vomiting or when it was apparent that his intake of fluids for the day was inadequate (i. e., less than 3,500 cc.).

The patient was routinely given 5 grains (0.32 Gm.) of ferrous sulfate three times a day, 2 multivitamin capsules daily and 1 Gm. of sodium chloride three times a day. When the patient began to have a chill, blankets were applied for comfort. No hot water bags were used for warmth. Beginning either with the chill or with the first recording of a temperature of 100 F., the temperature, the pulse rate and the respiratory rate were recorded every half hour until the temperature fell below 100 F. Barbiturates and codeine were used to control restlessness and severe headache. A physical examination, partial or complete, was made every other day, or more frequently if indicated. A record of the patient's symptoms and of physical findings was kept on special forms so that the data could be analyzed easily.

The patient was allowed to have paroxysms until he accumulated at least forty hours of fever with the temperature at 104 F. or over. In almost all instances, eight or more paroxysms were necessary in order to accomplish this. In certain instances a spontaneous remission of fever and other symptoms occurred with or without the disappearance of parasitemia. Some of the patients who tended to have fever of the quotidian type were given 0.1 Gm. of Thio-bismol intramuscularly, in an effort to convert the fever into a tertian type. In general, this was accomplished when the Thio-bismol was given from sixteen to twenty-four hours before the expected paroxysm.[3] This was done for two reasons: First, fever of the quotidian type exhausted the patient much more rapidly than did that of the tertian type. Second, when fever of the tertian type was maintained, one "brood" of parasites had sufficient time to develop gametocytes before the fever treatment was terminated. The development of adequate gametocyte levels allowed the infection of additional lots of mosquitoes with the malarial strains under study. In a few instances it was necessary to bring the malaria

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2. This strain of P. malariae was supplied by Dr. Mark Boyd, Tallahasse, Fla.

3. Mayne, B., and Young, M. D.: The Technic of Induced Malaria as Used in the South Carolina State Hospital, Ven. Dis. Inform. **22**:271 (Aug.) 1941.

therapy to an end with quinacrine hydrochloride because of a complication, e. g., jaundice or extreme exhaustion.

RESULTS

Table 1 gives the data pertaining to the transmissions of malaria by blood inoculations and by mosquito bites. It will be noted that the transmission of P. vivax, or tertian, malaria by the bites of mosquitoes was highly successful in the white patients (99 per cent successes) but relatively unsuccessful in the Negro patients (83 per cent failures) even with several attempts at inoculation.

The difficulty in transmitting domestic strains of P. vivax to Negro patients is well known[3]; whether it is an inherent racial characteristic

TABLE 1.—*Transmissions of Tertian and Quartan Malaria*

I. By Mosquitoes Infected with P. Vivax	Race	Guadalcanal	New Guinea	Mediterranean
Number of strains transmitted......	......	4	8	3
Number of patients with neurosyphilis	White	13	62	26
Number of patients inoculated......	White	101	..	..
	Negro	23	..	..
Number of patients inoculated successfully, with development of tertian malaria	White	99*	99%	..
	Negro	4†	17%	..

II. By Blood Containing Trophozoites of the Same Strains of P. Vivax as in I ‡			
Number of strains transmitted.....................	2	2	2
Number of patients with neurosyphilis inoculated..	4	50	17
Number of patients inoculated successfully.........	4(100%)	48(96%)§	17(100%)

III. By Blood Containing a Trinidad Strain of P. Malariae Induced	
Number of patients inoculated successfully, with development of quartan malaria........	48¶
Number of patients inoculated unsuccessfully...	3

* Nine of these patients had to be inoculated more than once.
† Of the 19 "failures," all were inoculated more than once.
‡ All of the patients in this group were white, and the group represents the initial attempt at inoculation.
§ See comment in text.
¶ This includes 3 white patients.

or whether it has been conditioned by previous exposure to P. vivax malaria cannot be judged from our data. It can be stated, however, that this racial difference in response to inoculation was not due to technical factors. The high percentage of successful transmissions shown by the white patients (99 per cent) attests the excellent technic used by the members of the United States Public Health Service in charge of those transmissions.[1] The results which we obtained in the Negro patients with foreign strains of P. vivax are in disagreement with the statement of Butler and Sapero[4] that American Negroes are very susceptible to Pacific strains.

4. Butler, F. A., and Sapero, J. J.: Postwar Tropical Disease Problems in the United States, South. M. J. **38**:459 (July) 1945.

Altogether, 71 attempts were made to transfer P. vivax to white patients by blood transfusions, and 69 of them were successful. The 2 instances of failure are deserving of comment. Both patients had acquired P. vivax malaria while overseas. The first had his last attack sixteen days, and his last dose of suppressive quinacrine hydrochloride twelve days, before the attempted inoculation. He was observed for seventeen days, and the inoculation was considered unsuccessful. He was then reinoculated with the same strain, and malaria developed in twelve days. Whether this attack was brought about by the second inoculation or whether it was a relapse of the naturally acquired malaria cannot be stated. The second patient had his last malarial attack thirty-five days before the attempted inoculation. Malaria developed twenty-five days later and without further inoculation. Since truly successful inoculations have not been observed by us to have such prolonged incubation periods (table 2), it seemed reasonable to assume that the inoculation was unsuccessful and that the patient suffered a relapse of his naturally acquired malaria.

Forty-eight patients, 45 Negro and 3 white, were successfully inoculated with P. malariae, producing quartan malaria. In only 3 patients were the inoculations unsuccessful. No efforts were made to transmit by mosquito bites the parasites producing quartan malaria.

Prepatent [5] *and Incubation* [6] *Periods Following Inoculation.*—Although rather large variations occur in the prepatent and the incubation periods in different persons, it will be noted that the averages for these intervals show little difference between the different strains of P. vivax. Since data are not available as to the degree of infection in the mosquitoes, no definite conclusion can be drawn from any of the slight, though statistically significant, differences noted. It can be stated generally that an average of two weeks elapses before signs of malaria appear after mosquito inoculation of imported strains of P. vivax. In this study the shortest time noted for the development of clinical malaria after the bite of the mosquito was eight days; the longest, twenty days. Apparently, when the sporozoite form of the parasite is introduced into the human host by the mosquito, at least eight days are required before erythrocytic forms appear in sufficient numbers to be seen or to produce symptoms. This is in definite contrast to the finding that on several occasions after the introduction of the trophozoite forms of the parasite by blood inoculation clinical malaria with visible parasitemia developed one day after the inoculation. In general, however, a period of four to five days was required. Again, as in the groups with

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5. The prepatent period is defined as the period between the time of inoculation and the time of development of parasitemia as revealed in a malarial smear.

6. The incubation period is defined as the period between the time of inoculation and the time at which the temperature rises above 100 F.

mosquito-induced malaria, there were rather wide individual variations, the reasons for which are not obvious.

As is well known, the incubation period for quartan malaria is characteristically longer than that for tertian malaria. In this series and with the same method of inoculation the incubation period was at

TABLE 2.—*Prepatent and Incubation Periods in P. Vivax, or Tertian, Malaria*

	Number of Cases Analyzed	Prepatent Period *		Incubation Period	
		Range, Days	Average, Days	Range, Days	Average, Days
I. Mosquito-Induced Malaria					
Source of strains:					
Guadalcanal	15	10-19	12.9±0.4	11-20	14.3±0.4
New Guinea	53	8-19	13.5±0.2	8-19	14.2±0.2
Mediterranean	22	9-14	12.2±0.2	11-16	13.1±0.2
II. Blood-Induced Malaria					
Source of strains:					
Pacific	54†	1-11	4.2	1-16	4.5
Mediterranean	17	1-12	5.1	1-12	5.1
Trinidad (quartan)	40	6-35	15.5	6-35	15.5

* The lowest density of parasitization which may be recognized by examination of a smear is approximately 10 parasites per cubic millimeter (Boyd [17]).

† All but four of these were of the New Guinea strain.

TABLE 3.—*Incidence of Usual Clinical Manifestations in Patients with Primary Attacks of P. Vivax Malaria Who Were Not Treated*

	Pacific Malaria (101 Patients), per Cent	Mediterranean Malaria (35 Patients), per Cent
Headache	98	100
Backache	98	100
General aches	90	94
Weakness	97	100
Nausea	85	77
Vomiting	72	63
Diarrhea	17	17
Cerebral symptoms	13	8
Tinnitus	31	28
Abdominal pain, right side	33	14
Abdominal pain, left side	51	25
Abdominal pain, none	48	63
Abdominal tenderness, right side	25	17
Abdominal tenderness, left side	63	45
Abdominal tenderness, none	30	48
Spleen palpated	72	57
Liver palpated	62	34
Herpes labialis	48	40

least ten days longer. This finding is in agreement with the statements of Mayne and Young [3] and of others.

The Course of the Infection.—(a) Clinical Features: As stated previously, an effort was made to allow the patient to experience forty hours of fever with the temperature 104 F. or higher as the therapeutic minimum. This was achieved in from nine to twenty-eight days, with

an average of eighteen days, for P. vivax, or tertian, malaria, and in from fourteen to thirty-one days, with an average of twenty-two days, for quartan malaria. From eight to fifteen paroxysms were required to obtain the desired result. Certain patients, however, never attained the desired amount of fever, because a spontaneous remission aborted the attack. This interesting phenomenon will be commented on later.

Table 3 lists the most common clinical symptoms and signs of the untreated patients with primary attacks of P. vivax, or tertian, malaria. No patients with quartan malaria were included in this analysis. The features noted are not considered as complications of the disease since they appeared to be characteristic of the infection itself. Headache, backache, generalized aching and varying degrees of weakness were present in practically all the patients whether the disease was of Pacific or of Mediterranean origin. Gastrointestinal complaints also were common; nausea and vomiting were present in about three fourths of the patients during some period of the illness. Abdominal pain, usually in the upper quadrant, and tenderness appear to be somewhat less frequent in malaria of Mediterranean origin than in that of Pacific origin, but the number of patients studied in detail in the former group was small. Tinnitus was noted in more than one fourth and herpes labialis in almost half of the patients. It would seem that in some patients suffering from natural malaria the auditory disturbances which have been noted and attributed to gunfire or to the administration of quinine may have been due to the malarial infection itself.

Hepatic enlargement and splenic enlargement were common and were noted somewhat more frequently in malaria of Pacific origin. In an analysis of the frequency with which splenic and hepatic enlargement occurred during the promptly treated acute attacks of naturally occurring relapsing P. vivax malaria of Pacific origin, it was found that the spleen was palpable in only 23 per cent and the liver in 11 per cent.[7] The fact that in the total series splenomegaly and hepatomegaly were noted in 72 and 62 per cent of the patients, respectively, is accounted for by the longer duration of the untreated illness. In figure 1 it will be noted that the longer the period of malarial activity the more likely was the spleen or the liver to be palpable.

Cerebral symptoms were noted in at least 10 per cent of all patients and appeared to be of no more serious import than those seen in any other severe febrile illness. In other words, no patients could be considered to manifest the features of "cerebral malaria" caused by P. falciparum infections. In all patients the cerebral symptoms disappeared

7. Gordon, H. H.; Lippincott, S. W.; Marble, A.; Ball, A. L.; Ellerbrook, L. D., and Glass, W. W., Jr.: Clinical Features of Relapsing Plasmodium Vivax Malaria in Soldiers Evacuated from the South Pacific Area, Arch. Int. Med. **75**:159 (March) 1945.

as soon as the body temperature fell to normal levels. A semistuporous state or mild mental confusion was the most usual symptom; however, delirium was noted in 2, and unconsciousness in 3, different patients.

PER CENT OF
TOTAL PATIENTS

• PALPABLE SPLEEN
× PALPABLE LIVER

DAYS   4   8   12   16   20   24   28
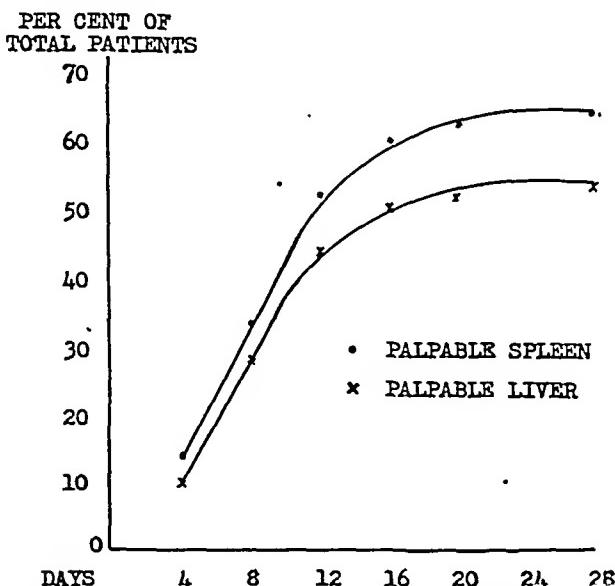
Fig. 1.—The relation of the occurrence of hepatomegaly and splenomegaly to the duration of the illness.

PARASITES/CU. M.M.

⊞ NEGATIVE   ■ 5001–10,000
□ < 1000   ▦ > 10,000

PER CENT
OF CASES   ▨ 1001–5000.   •—• PER CENT OF ORIGINAL CASES DROPPED

DAY OF   1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
ILLNESS
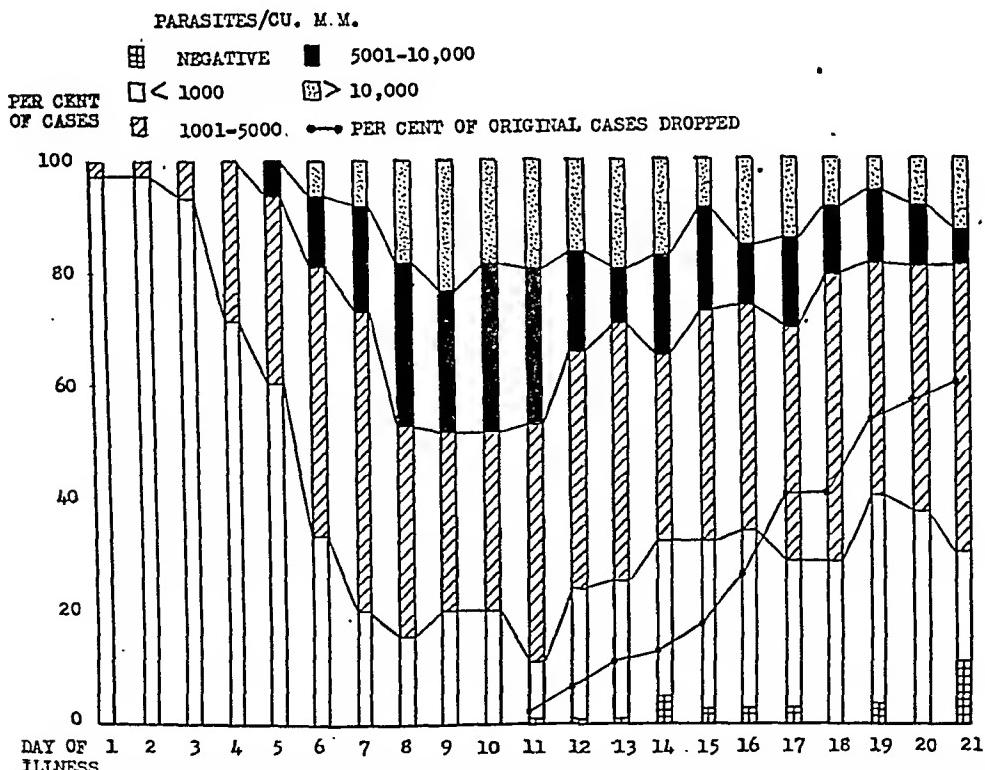
Fig. 2.—The relation of the percentage distribution of densities of parasitization of the blood to the day of disease in sporozoite-induced Pacific P. vivax malaria.

(b) Degree of Parasitemia: A careful analysis was made regarding the trend of the densities of the parasitizations in 46 patients. These

patients had been mosquito-inoculated with Pacific strains of P. vivax, and in this group no effort had been made to influence the course of the infection in any way—e. g., by the administration of Thio-bismol. Figure 2 shows in graphic form the data obtained. On the first day that the parasites were observed in smears, only 4 patients had a sufficient degree of parasitemia to allow an actual count; the remaining 42 patients had merely "positive thick smears." It will be noted that after the second day a fairly rapid rise occurred in the parasite counts, so that a peak was reached by about the eleventh day. Thereafter there was a gradual but definite fall. This is more easily seen in figure 3, in which the data on density of parasitization are presented as total averages rather than as percentage distribution. The data were not analyzed beyond a three week period, since by this time in over half the cases the desired therapeutic effect had been reached and the patients
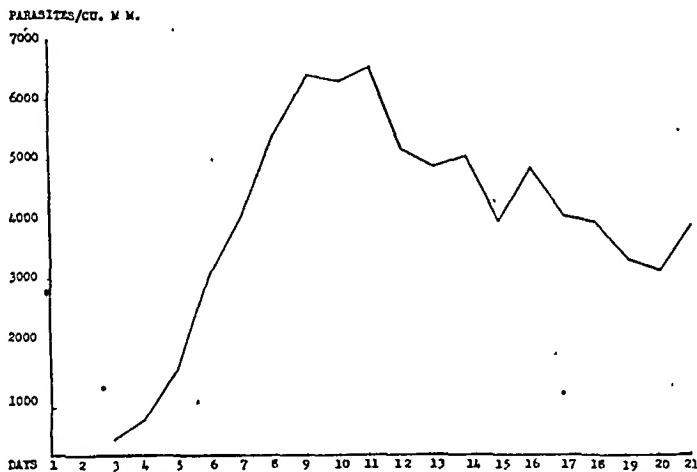
Fig. 3.—The relation of average densities of parasitization to the day of disease in sporozoite-induced Pacific P. vivax malaria.

had been started on quinacrine hydrochloride, leaving too few cases for analysis. It appears that most persons suffering from the primary attack of tertian malaria acquire some degree of immunity after the first few days of the infection, shown by the fall in parasitic densities.[8]

(c) Occurrence of Spontaneous Remissions: As stated by Boyd, Kiepper and Matthews,[9] varying degrees of immunity or susceptibility will be indicated by the responses of patients to inoculation. Earlier in the paper it was mentioned that only a small percentage of the Negro

8. Taliaferro, W. H., and Taliaferro, L. G.: Active and Passive Immunity in Chickens Against Plasmodium Lophurae, J. Infect. Dis. **66**:153, 1940; The Effect of Immunity on the Asexual Reproduction of Plasmodium Brasilianum, ibid. **75**:1, 1944.

9. Boyd, M. F.; Kiepper, W. H., and Matthews, C. B.: A Deficient Homologous Immunity Following Simultaneous Inoculation with Two Strains of Plasmodium Vivax, Am. J. Trop. Med. **18**:521, 1938.

patients were successfully inoculated with P. vivax. Presumably those persons in whom inoculation failed possess the highest degree of immunity. In figure 4 are shown typical examples of varying degrees of clinical tolerance of the malarial parasites. The first patient had "positive thick smears" for four days, underwent one mild malarial paroxysm and then not only became completely asymptomatic but possessed sufficient immunity to cause the visible parasitemia to disappear. The other patient had a spontaneous remission after six satis-
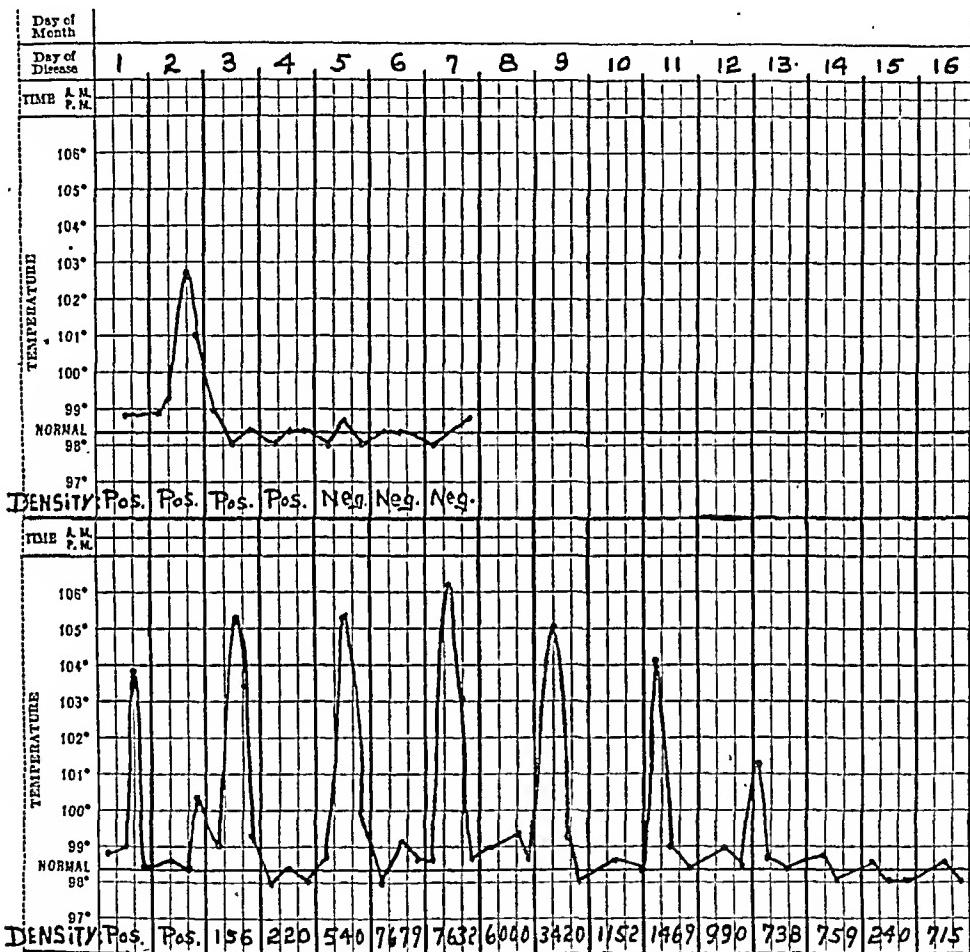
Fig. 4.—Two examples of spontaneous remissions in induced P. vivax malaria.

factory paroxysms although still maintaining fairly good densities of parasitization. In fact, these densities were as great as, or greater than, those observed earlier in the illness while good paroxysms were occurring. Apparently the occurrence of the malarial paroxysms depends more on the presence or the absence of immune mechanisms and/or the stage of development of the parasite than on the number of parasites present in the blood. This is supported by the fact that we were unable to demonstrate a significant correlation between the number of hours of fever on any given day and the density of parasitization. The variable rela-

tion between parasitic density and number of paroxysms has been discussed for *P. falciparum* malaria by Kitchen.[10]

In an effort to determine whether or not a previous attack of malaria played any part in the development of the spontaneous remission, careful past histories were obtained from the 172 patients inoculated with P. vivax. The data thus obtained are shown in table 4. Spontaneous remissions were observed more than three times as frequently in those who gave a past history of malaria than in those who did not. Therefore, it seems reasonable to believe that previous attacks of malaria may confer a certain degree of immunity as manifested by spontaneous remissions. However, that this immunity was incomplete is shown by the fact that it was possible to transmit the infection to almost all the white patients.

TABLE 4.—*The Relation of Spontaneous Remissions to a Past History of Malaria in One Hundred and Seventy-Two White Patients Successfully Inoculated with P. Vivax*

	Total	Number Having Remission	Per Cent Having Remission
Without past history of malaria....................	145	31	21
With past history of malaria......................	27	19	70

Since this Army hospital was located in the southern part of the United States, where malaria is more or less endemic, and since there was a certain regional admission of patients with neurosyphilis, a higher percentage (16 per cent) of our patients gave a past history of malaria than might, be observed in other parts of the country. Twenty-two of the 27 patients with such a history had had malaria during civilian life, usually many years prior to the course of therapeutic malaria. It seems that once a certain degree of tolerance of the malarial parasites is developed it is not soon lost but may persist for many years. Of the 5 patients who had acquired malaria naturally during their Army career, 2 underwent a spontaneous remission during the course of therapeutic malaria.

Complications.—In table 5 are summarized the complications noted in both the tertian and the quartan forms of malaria. Of 172 patients suffering from untreated P. vivax malaria, 28 had albuminuria (16 per cent). None of these had albumin graded more than "2 plus" (on a scale of 4) in their urine, and the presence of albumin was not associated with occurrence of abnormal elements in the urinary sediment

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10. Kitchen, S. F.: The Infection in the Intermediate Host, Symptomatology, Falciparum Malaria, in A Symposium on Human Malaria, Publication 15, American Association for the Advancement of Science, 1941, p. 196.

or with evidence of renal insufficiency. Furthermore, with termination of fever the albuminuria disappeared.

However, 3 Negro patients suffering from quartan malaria had moderate azotemia, marked albuminuria and hyaline and granular casts in the urinary sediment. In none did hypertension, evident edema, retinal change or anemia develop. All 3 patients had normal urine on two examinations and normal levels of nonprotein nitrogen in the blood before the fever began, and none gave a past history of disease of the urinary tract. One of these patients had to be transferred to another hospital twelve days after the termination of the fever therapy. At the time of transfer albumin and formed elements were still present in the urinary sediment, although the nonprotein nitrogen of the blood had fallen from a maximum of 120 mg. per hundred cubic centimeters to

TABLE 5.—*Complications Noted During the Course of Therapeutic Malaria*

	P. Vivax, or Tertian, Malaria (172 Patients)		Quartan Malaria (48 Patients)	
	Number	Per Cent	Number	Per Cent
Albuminuria (benign)...................................	28	16	..	..*
Jaundice...	8	5	1	2
Severe anemia (red blood cell count below 3,000,000)......	11	7	(No record)	
Urticaria..	4	2	0	0
Dependent edema.......................................	2	1	0	0
Hiccups...	3	2	0	0
Dendritic corneal ulcer.................................	1	0.5	0	0
Pulmonary tuberculosis.................................	1	0.5	0	0
Uremia..	0	0	3	7
Deaths..	0	0	0	0

* Records are available for only 15 patients; 4 were shown to have transitory albuminuria. In the urine of 1, however, albumin did not completely disappear and is still present in slight amounts, two and a half months after making its appearance. This patient also was shown to have moderate elevations of blood cholesterol level (375 and 400 mg. per hundred cubic centimeters), but there were no evidences of nitrogen retention, edema or inability to concentrate the urine.

normal and the blood cholesterol was 150 mg. per hundred cubic centimeters. Subsequent data on this patient are not available. However, the second patient first showed abnormal urine after eight paroxysms, and the nonprotein nitrogen in the blood rose to a maximum of 120 mg. per hundred cubic centimeters seven days later. A pure culture of the gonococcus was obtained from the urine, but the exact focus of infection was not determined. There was no urethral discharge; the prostate was normal on examination, and after a later course of penicillin the urine no longer yielded positive cultures. However, before the penicillin treatment was started and after the antimalarial treatment with quinacrine hydrochloride was instituted, the albuminuria disappeared and the nonprotein nitrogen in the blood fell to normal levels. It appears that the renal insufficiency was due to the malaria rather

than to the infection of the urinary tract. Likewise, the azotemia appeared to be of renal origin and not "extrarenal," since evidences of renal damage were so conspicuous in the urine and since the blood pressure and the fluid balance appeared to be maintained throughout the illness.

In the third patient the abnormal findings appeared after the second malarial paroxysm; the nonprotein nitrogen in the blood was 50 mg. per hundred cubic centimeters three days later and rose to a maximum of 130 mg. ten days after the appearance of albuminuria and five days after the quinacrine therapy was started. In contrast to the second patient, the third patient had azotemia associated with a moderate suppression of urinary output and a fall in specific gravity of the urine for four days prior to the maximal azotemia. The urinary output ranged from 660 to 1,060 cc. on intakes of 3,360 to 4,560 cc. per day. The patient was not having fever during this period, and edema was not evident. With intravenous injection of fluids and the disappearance of malarial parasites from the blood cells as shown by examination of smears, the nonprotein nitrogen gradually fell to normal. · Three and one-half weeks later the patient was completely asymptomatic, although he still had moderate albuminuria and was unable to concentrate urine to a specific gravity above 1.020. The blood cholesterol values determined after the nonprotein nitrogen had reached normal levels were 300 and 261 mg. per hundred cubic centimeters, and the values for serum proteins were normal. Apparently, in the patients studied quartan malaria was more apt to cause serious renal damage than was tertian malaria. The incomplete data available on these patients do not warrant speculation as to the nature of the renal lesion. However, Kitchen[11a] and Meleney[11b] have both pointed out that a picture of the nephrotic syndrome is sometimes observed in patients suffering from chronic quartan malaria and more rarely in those suffering from P. vivax malaria. It is reported that in some of the patients with renal involvement the disease has gone on to a fatal termination despite antimalarial therapy. Also, Giglioli, cited by Meleney, observed 5 patients with quartan malaria who died and who presented the picture of chronic glomerular nephritis with nitrogen retention.

Recognizable jaundice occurred in 8 patients with P. vivax, or tertian, malaria and in 1 patient with quartan malaria. The jaundice appeared from nine to twenty-five days after the onset of the illness. On its appearance, the fever was terminated with quinacrine hydrochloride. In all the cases the jaundice appeared to be due to hepatitis directly caused by the malarial infection. The liver was enlarged and

11. (*a*) Kitchen, S. F.: The Infection in the Intermediate Host, Symptomatology, Quartan Malaria, in A Symposium on Human Malaria, Publication 15. American Association for the Advancement of Science, 1941, p. 190. (*b*) Meleney, H. E.: The Physiological Pathology of Malaria, ibid., p. 223.

tender; bile was present in the urine, and the direct van den Bergh test showed an immediate or delayed reaction. In 1 instance the jaundice developed when there was a spontaneous remission of his fever, but the blood smears revealed evidence of malaria. In all instances, terminating the infection and giving the patient supportive treatment (dextrose solutions intravenously, extra amounts of vitamins, a high protein diet) resulted in rather rapid disappearance of the jaundice and the enlargement of the liver. In table 6 are given the available data from the studies of hepatic function in these patients. A detailed report on changes in hepatic function in patients with induced malaria has been presented recently by Fredricks and Hoffbauer,[12] and the results of other studies will be considered in detail in a separate communication.

In most of the patients there was moderate anemia (the number of red blood cells ranging between 3,000,000 and 4,000,000 per cubic millimeter), but severe anemia (red cell counts less than 3,000,000) was noted in only 11 of the patients with P. vivax malaria. In 1 patient the anemia and the exhaustion were of sufficient degree to warrant a blood transfusion. We have no accurate data concerning the rate of disappearance of the anemia since the patients were given a three week convalescence furlough after they had received complete treatment with quinacrine hydrochloride. However, in most instances normal erythrocyte counts were observed on the patients' return to the hospital.

Generalized urticaria was noted in 4 patients. It was not particularly severe, nor was it associated with edema of the glottis. In all instances it made its appearance within the first five days of illness and disappeared within three days.

Edema of the ankles was noted in 2 patients. In 1 of these patients the serum proteins were determined and were found to be somewhat below normal; the total protein was 5.5 Gm., the albumin 2.7 Gm. and the globulin 2.8 Gm. per hundred cubic centimeters. In this patient mild jaundice was noted about the same time that edema of the ankles appeared. After the fever therapy was discontinued and the patient's general condition improved, the jaundice and the edema disappeared. At no time did the patient have albumin in his urine. The hypoproteinemia may have been due to hepatic damage and/or diminution of the intake of protein.

Severe hiccups developed in 3 patients. The cause was not entirely clear, but in all there was moderate abdominal distention. The hiccups were controlled by morphine, warm stupes to the abdomen and neostigmine bromide after the usual measures failed to bring relief.

12. Fredricks, M. F., and Hoffbauer, F. W.: A Study of Hepatic Function in Therapeutic Malaria, J. A. M. A. **128**:495 (June 16) 1945.

TABLE 6.—*Summary of Results of Tests of Hepatic Function in Eight Patients Who Contracted Clinical Jaundice During Fever Therapy with P. Vivax Malaria*

Patient	Initial Studies *						During Fever						Liver			After Fever						Clinical Evidence of Hepatic Disease
	I.I.	S.B.	Brom.	Hipp.	Galact.	Uro.	I.I.	S.B.	Brom.	Hipp.	Galact.	Uro.	Enl.	Ten.	Vomiting	I.I.	S.B.	Brom.	Hipp.	Galact.	Uro.	
L.L..........	5	0.1	Trace	..	0.45	1:5	50	8.0	..	..	..	1:100	2+	2+	0	7	0.4	3	..	0.2	1:5	None
O.L...........	7	0.2	2	..	0.71	1:5	80	8.1	..	..	..	1:100	2+	2+	Yes	..	..	2	..	1.0	1:20	None
C.M..........	5	0.3	2	..	0.56	1:5	60	2.5	40	..	..	1:200	1+	2+	Yes	8	1.0	2	..	..	...	None
V.V.........	10	1.0	Trace	..	1.65	1:20	35	2.0	..	..	..	1:100	1+	1+	0	7	2.0	Neg.	..	..	1:5	None
E.H...........	9	0.7	4	0.9	....	...	30	2.0	32	0.23	0.59	.....	1+	1+	0	..	..	2	..	..	...	None
A.B...........	7	0.2	2	1.0	....	...	36	2.2	36	0.3	..	.....	1+	1+	0	..	..	2	0.58	..	...	None
C.W...........	..	..	......	..	....	...	50	2.8	..	..	..	.....	2+	0	Yes	..	..	..	..	..	...	None
J.D...........	..	..	......	..	....	...	80	5.6	..	..	..	.....	1+	0	0	..	..	..	..	..	...	None

* The Icterus Index (I.I.) is recorded in units and the serum bilirubin (S.B.) in milligrams per hundred cubic centimeters. The sulfobromophthalein sodium retention (Brom.) is recorded as per cent retained in the specimen of blood taken forty-five minutes after the injection of 5 mg. of the dye per kilogram of body weight. The bippuric acid tolerance is recorded as the gram of hippuric acid present in the specimen of urine collected for one hour following the intravenous injection of 1.77 Gm. of sodium benzoate. The galactose tolerance (Galact.) is reported as the amount of galactose excreted in the urine during a five hour period after the ingestion of 40 Gm. of galactose. The urobilinogen excretion (Uro.) is recorded as the concentration in a single morning specimen of urine.

In 1 patient a dendritic ulcer of the cornea developed, which persisted for three weeks after the cessation of fever. It is interesting that this patient did not have associated herpes of the lip.

One patient contracted acute pulmonary tuberculosis during the course of the fever therapy. This was the most serious complication encountered. The patient had a normal chest before beginning treatment, according to a roentgenogram taken at that time. A small exudative lesion was discovered during a routine 'roentgenologic examination one month after the malaria therapy was terminated.

No deaths have occurred in this series of patients. Moore [13] reported, from his own experience and from a survey of the literature, a mortality rate of from 1 to 2 per cent among selected patients given P. vivax malaria. Fong [14] reported a mortality rate of 2.9 per cent among patients treated with quartan malaria. That we were fortunate enough not to have any deaths can be accounted for by the fact that most of the patients were young, healthy men whose neurosyphilis was asymptomatic and also by the fact that careful examinations were made to rule out renal, hepatic or cardiac disease and adequate care given during the course of the fever.

Rate of Disappearance of Parasites with Quinacrine Hydrochloride.— When adequate malarial therapy had been completed, all the patients were treated with quinacrine hydrochloride. The dosage was essentially as previously described,[15] namely, 0.8 Gm. the first twenty-four hours and 0.4 Gm. each twenty-four hours for five subsequent days, so that a total of 2.8 Gm. was given in six days. By the second day—i. e., forty-eight hours after the beginning of therapy—96 per cent of the patients had become afebrile. It is noted from figure 5 that practically all the patients (96 per cent) suffering from P. vivax malaria, whether this was mosquito induced or blood induced, had negative smears by the third day—i. e., seventy-two hours after the beginning of antimalarial therapy. In an analysis of data on 111 patients with induced P. vivax malaria in whom the actual density of parasitization was known the day prior to starting antimalarial therapy it was found that, in general, those patients with lower densities had negative smears before those with higher densities. This is shown in figure 6 and is similar to what is found in studies of naturally acquired P. vivax malaria of foreign origin.[16] It is also of interest that only 21 per cent of smears

13. Moore, J. E.; Kemp, J. E., and others: The Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943, p. 389.

14. Fong, T. C. C.: Therapeutic Quartan Malaria in Therapy of Neurosyphilis Among Negroes, Am. J. Syph., Gonor. & Ven. Dis. **24**:133, 1940.

15. Treatment of Clinical Malaria and Malarial Parasitemia, Bull. U. S. Army M. Dept. **4**:284 (Sept.) 1945.

were free of parasites twenty-four hours after treatment was begun (fig. 5), compared with 51 per cent in a group of patients with relapses of the naturally acquired disease.[16] This is probably due to the higher percentage (46 per cent) of patients with parasitic densities
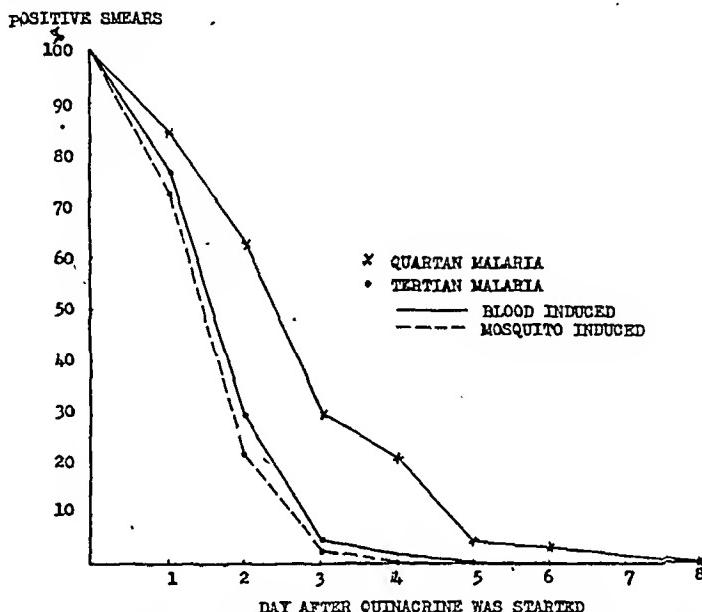
Fig. 5.—The rate of disappearance of parasites with administration of quinacrine hydrochloride in the customary dosage.
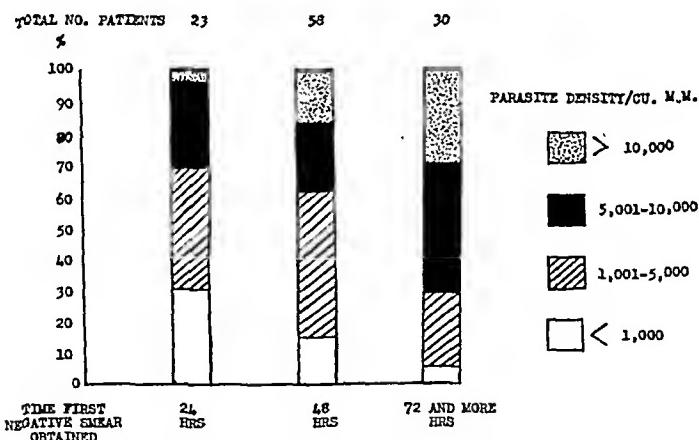
Fig. 6.—The relationship of parasitic density before treatment to the time at which the first smear free of parasites was obtained.

above 5,000 per cubic millimeter in this study, compared with 22 per cent among patients with naturally acquired malaria.[16]

Figure 5 also reveals that visble parasitemia is definitely slower in its disappearance in patients having quartan malaria than in those

16. Gordon, H. H., Christianson, H. B., and Lippincott, S. W.: A Comparison of Quinine and Quinacrine in the Treatment of the Clinical Attacks of Vivax Malaria, South. M. J. **39**:631 (Aug.) 1946.

having tertian malaria. For example, by the third day of quinacrine therapy almost all patients suffering from tertian malaria had negative smears while approximately 30 per cent of those with quartan malaria still had positive smears. In fact, for 1 patient the quinacrine therapy had to be continued past the sixth day, and the smears did not become free of parasites until the eighth day. Unfortunately, actual densities of parasitization are not available for this group of patients. The existence of this difference in response to quinacrine may reside in biologic differences between the two species of parasites. This is believed to be true because much higher densities are encountered· in tertian (P. vivax) than in quartan (P.'malaria') malaria.[17]

Relapse Rates of Induced Malaria.—No data were obtained on the relapse rates of quartan malaria. In table 7 is given a summary of

TABLE 7.—*Relapses Following Quinacrine Treatment of Induced P. Vivax Malaria of Foreign Origin*

	Total Number of Patients	Number of Patients Who Relapsed*	Per Cent of Patients Who Relapsed	Observation Period of Nonrelapsers, Days
Pacific "Mosquito-induced"	69	45	65	109 (66-185)
Pacific "Blood-induced"	28	0	0	106 (66-165)
Mediterranean "Mosquito-induced"	16	2	13	113 (61-162)
Mediterranean "Blood-induced"	4	0	0	82 (64-95)

* No patient was considered a nonrelapser unless he had been followed for at least sixty days after completion of quinacrine therapy.

information in ·regard to P. vivax malaria. These data are discussed in more detail in a separate report.[18] Suffice it to state that no relapses were observed in the group with blood-induced malaria, while a relapse rate of 65 per cent was recorded for the group with mosquito-induced infection, similar strains of P. vivax of Pacific origin being used. This indicates, as has been well known for other strains, that the introduction of trophozoites of Pacific P. vivax was not followed by a relapsing disease but the introduction of sporozoites was. In a small group of 16 patients with mosquito-induced malaria of Mediterranean origin there were only 2, or 13 per cent, relapses within the period of observation. Apparently, within the period noted, Mediterranean malaria did not have the same stubborn tendency to relapse as Pacific malaria.

17. Boyd, M. F.: Present Day Problems of Malaria Infections, J. A. M. A. **124**:1179 (April 22) 1944.

18. Gordon, H. H.; Marble, A.; Engstrom, W. W.; Brunsting, H. A., and Lippincott, S. W.: Relapses Following Delayed Treatment of Naturally Induced Vivax Malaria of Pacific Origin, Science **103**:391 (March 29) 1946.

SUMMARY AND CONCLUSIONS

In 195 patients (172 white and 23 Negro) with neurosyphilis attempts were made to transmit Plasmodium vivax malaria by mosquito bites or by inoculation of blood. The strains transmitted were of Pacific and Mediterranean origin.

The attempts to transfer P. vivax malaria whether by mosquito bites or by inoculation of blood were highly successful in white patients, whether they gave a past history of malaria or not, and relatively unsuccessful in Negro patients. However, a spontaneous remission of fever was observed more than three times as frequently in those who gave a past history of malaria as in those who did not.

The prepatent [5] and incubation [6] periods averaged about two weeks when mosquitoes, and five days when blood, was used in the transmission of the infection.

It was noted that as the disease progressed the concentration of parasites in the blood at first rapidly increased but after the eleventh day began to fall.

Sixty-five per cent of the patients inoculated by mosquitoes infected with Pacific strains of P. vivax had relapses, while no patients relapsed who had been inoculated intravenously with blood containing the same strains.

Quartan malaria was transmitted to 48 patients (45 Negro and 3 white) by inoculation of blood containing P. malaria. Quartan malaria differed from tertian (P. vivax) malaria not only in the longer interval between paroxysms but also in the longer period of incubation, the slower response to quinacrine therapy and the tendency to cause serious renal complications.

No deaths were seen in this series of patients.

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ACTINOMYCOTIC ENDOCARDITIS

Report of Two Cases with a Review of the Literature

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CARDIAC involvement produced by Actinomyces is not frequently reported in medical literature. Cornell and Shookhoff [1] have presented a comprehensive review of 68 cases. Recapitulation of such a review is not within the scope of this paper. Actinomycotic endocarditis without trace of related disease in any other part of the body is rare.

REVIEW OF THE LITERATURE

Jervell [2] reported a case of endocarditis with the etiologic agent determined as a leptothrix which was recovered in pure culture from the blood.

The patient was a 20 year old man with a history of rheumatic fever at 12 years of age and with cardiac involvement on subsequent occasions. Three weeks before the last admission to the hospital, acute gastroenteritis developed, followed by symptoms of pyemia and myelitis. Ecchymosis and numerous petechiae appeared in various organs. Systolic and diastolic murmurs were present, and extra systoles occurred. The urine contained albumin, pus, blood and urobilin. In the laboratory it was not possible to recover from the urine the gram-positive rods in pure culture. A blood count showed 70 per cent hemoglobin (Sahli), 4,200,000 erythrocytes per cubic millimeter and 20,000 leukocytes per cubic millimeter. Spinal puncture revealed a slightly cloudy fluid with about 150 cells per cubic millimeter, of which about 50 per cent were lymphocytes and 50 per cent were polymorphonuclear leukocytes. Tests for albumin and globulin were positive. Cultures were sterile. Ophthalmoscopic examination of the eyegrounds produced evidence of "Embolia art. retinae" near the macula lutea of the left eye. This was associated with paracentral scotoma. Weakness and then paresis of both legs developed. Urinary incontinence occurred. There was pain about the nates and the anus. Anesthesia was present from the lumbar region downward. Babinski's reflex was present. Various neurologic examinations showed shifting signs from time to time. Before death, complete right-sided hemiplegia developed with aphasia and coma. The patient died about six weeks after the onset of illness.

An anatomic summary of the autopsy revealed: "Endocarditis verrucosa valv. mitralis et aortae. Hypertrophia et dilatatio cordis. Haemorrhagia punctatae (et emollitio) cerebri. Embolia art. fossae Sylvii dext. Infarctus et abscessus lienis.

1. Cornell, A., and Shookhoff, B.: Actinomycosis of the Heart Simulating Rheumatic Fever, Arch. Int. Med. **74**:11-27 (July) 1944.

2. Jervell, O.: Leptotrix i blodet ved et tilfælde av malign endokardit, Norsk mag. f. lægevidensk. **83**:36-46, 1922.

Infarctus renis sin. Degeneratio parenchym. hepatis." All three aortic leaflets and both mitral leaflets showed verrucous vegetations. Ulcerations were present in association with the lesions of the mitral leaflets. Sections of valvular lesions showed gram-positive rods. The author considered the possibility of the symptoms of myelitis being associated with the emboli present in the medulla.

Plate cultures of blood showed small gray-white colonies with faint zones of hemolysis. Microscopically, the organism occurred as gram-positive rods. Broth cultures showed the organism developing gram-positive filaments without ramifications. The organism was aerobic and did not grow anaerobically. The rods were referred to as small, almost simulating streptococci, for which they were first mistaken. Micro-organisms similar to those of the blood cultures were recovered from the lesions of the heart valves and the spleen, but not in pure culture. Cultures were inoculated into guinea pigs, white mice and rabbits, without results.

Alestra and Girolami[3] reported 2 cases with the clinical picture of subacute endocarditis, in neither one of which was there any evidence of a portal of entry.

The first patient was an 18 year old barber with a previous history of having had intermittent fever from 8 to 10 years of age, at which time pleurisy of the right side developed. After this incidence, fever did not recur, and the patient remained in good health except for dyspnea on exertion. At 18 years of age he had an attack of sore throat, malaise, chills, fever and palpitation. The spleen was palpably enlarged. A roentgenogram of the heart showed particular enlargement of the left border. A blood count showed 18,000 leukocytes per cubic millimeter, 81 per cent of which were polymorphonuclear leukocytes. Two blood cultures were positive for the same type of organism, which occurred as greenish brown pinpoint colonies, similar in appearance to those of Streptococcus viridans. The colonies were similar microscopically to those in broth cultures. The organism took a gram-variable stain and appeared as cocci, streptococci, coccobacilli, rods and filaments. No branching forms were seen. Subcultures failed to show growth, and anaerobic cultures were not carried out. The authors expressed the belief that they were dealing with a streptothrix, although they mentioned that the organism was not studied completely, because of its failure to grow.

The patient was treated with iodides. He also received a total of 480 cc. of Septojod (a preparation of iodine for parenteral use) intravenously. No fever developed at the end of treatment, and the spleen was no longer palpated. The systolic murmur had become louder. He was followed for two years, during which there was no development of illness. After this period he was lost.

The second patient was a 37 year old woman employed as a clerk, with the history of having had sore throat on two occasions two years apart. She was treated with diphtheria antitoxin. At 11 years of age she was told by a physician that she had a congenital heart disease. At 13 years of age she had exudative pleurisy on the right side. After this she was in good health up to the age of 25. At this time she had an attack of palpitation, cyanosis of the face, tremors and dizziness. She never lost consciousness. The attack was of short duration and was followed by headaches. At 32 years of age she experienced sore throat, fleeting pains, chills and sweats. The sore throat cleared up in eight days under treatment with salicylates. Later palpitation and cardiac arrhythmia with extra

3. Alestra, L., and Girolami, M.: Endocarditi da nocardie, Policlinico (sez. med.) **44**:441-463, 1937.

systoles developed. When she was 37 years old, she experienced anorexia, general malaise, a sudden severe pain in the left side of the chest and a few days later a fever. She was given a proprietary 1 per cent solution of sodium iodide intramuscularly; fever and sore throat persisted, although the thoracic pain disappeared. The heart was enlarged transversely. An intensive systolic thrill was present over the midsternal line and was palpated in the second intercostal space. The blood pressure was 98 mm. of mercury systolic, and 65 diastolic. A blood count showed 24,000 leukocytes per cubic millimeter. Progressive cardiac impairment developed, and the patient died about five months after the onset of the last illness, with a clinical diagnosis of subacute endocarditis with congenital heart disease. She had received sulfonamide drugs by mouth, sodium salicylates, Prontosil (the hydrochloride of 2,4-diaminoazobenzene-4-sulfonamide), a total dose of 100 cc. of Septojod intramuscularly, arsenical preparations and cardiotonics.

Autopsy showed hypertrophy of the right ventricle and vegetative endocarditis involving the pulmonary valves and conus. The borders of the defects showed thickening consistent with previous endocarditis. Patency of the interventricular septum was present below the aortic ring. A small anemic pulmonary infarct and pleurisy with adhesions were also present. Microscopically, the endocardium was infiltrated with small thrombi. The vegetations showed small abscesses and groups of coccal forms and bacillary elements.

Five blood specimens cultured showed pinpoint gray colonies that developed in four hours, after which no further development occurred. Subcultures, however, in dextrose agar showed moist firm white colonies that were adherent to the medium. These had a greenish color on plain agar. Microscopically, the organism occurred as cocci, arranged in groups and in chains, from some of which elongated and fusiform structures extended. Bacillary forms and straight and flexed filaments were present. Some filaments contained granules along their entire extent and stained as if composed of gram-positive cocci in gram-negative filaments. The organism took a gram-variable stain.

A culture was inoculated into guinea pigs and rabbits. The animals died within twenty-four hours. The same organism was recovered in culture from the animals. The authors considered this organism as "Nocardia."

Uhr[4] observed endocarditis due to Actinomyces bovis in a 24 year old Jewish man. No other focus of infection was found to suggest a portal of entry.

The patient became ill with pain in both calves, nausea, vomiting and malaise, followed by fever, chills and sweats. A short systolic murmur was localized over the apex. The heart rate was 120. The cardiac sounds were forceful and regular. During his stay in the hospital the systolic murmur became aggravated. Petechiae and larger purpuric lesions developed over various parts of the body. The sensorium became clouded, and coma ensued. The patient died thirty-five days after the onset of illness. Treatment consisted of supportive measures, transfusions, administration of oxygen and intravenous injection of sodium diiodide. which was discontinued in absence of adequate response.

Four separate blood specimens cultured while the patient lived yielded a pure culture of A. bovis. The organism grew only in presence of blood and was micro-aerophilic. It required reduced oxygen tension for isolation. Culturally, the organism showed up as "tangled threads of mycelium." Older cultures showed

4. Uhr, N.: Bacterial Endocarditis: Report of a Case in Which the Cause Was Actinomyces Bovis, Arch. Int. Med. **64:**84-90 (July) 1939.

many abnormal structures. The organism was not acid fast and was gram positive. The strain was not pathogenic for rabbits.

At autopsy the mitral valve presented a large soft friable yellowish vegetation which principally involved the aortic cusp, but small clusters were also along the line of closure. The anterior and posterior surfaces of the cusps of the mitral valve were involved for some distance. There was no evidence of previous valvulitis. The left auricle showed a small vegetative endocardial lesion, but there was no evidence of an old rheumatic auricular lesion. Microscopic section of the spleen showed "a bacterial clump" in an arteriole. Cultures of the crushings of the mitral lesion showed A. bovis.

Basu [5] mentioned a strain of Actinomyces recovered from the blood stream of a patient on the ninth day of an illness with high fever and patches of bronchopneumonia in both lungs. This was an aerobic organism which produced no lesions in rabbits.

Cornell and Shookhoff [1] referred to a case diagnosed clinically as one of rheumatic heart disease in both the Norwegian Hospital and the Montefiore Hospital, where the patient was observed for several months. Autopsy revealed myocardial and pericardial actinomycosis. This involvement, however, was by extension from the original source in a diverticulum of the esophagus.

REPORT OF CASES

CASE 1.—A 37 year old married white man, born in Minnesota, had been on the Isthmus of Panama for twenty-nine months in the capacity of switchboard operator at Gatun Hydroelectric Power Station. He was admitted to a Canal Zone hospital, Dec. 26, 1942, with marked pallor, discrete small nontender palpable nodes in both inguinal regions, elevated temperature and a rasping systolic murmur over the apex of the heart. This murmur was faintly transmitted along the sternum. No enlargement of the heart was evident, and no arrhythmia was noted. The blood pressure was 110 mm. of mercury systolic and 70 diastolic. No petechiae were observed. The previous personal history was negative except for growing pains in the legs for one month at the age of 6 years. The family history was noncontributory. A diagnosis of acute bacterial endocarditis was made; the blood cultures, however, were sterile.

Course in Hospital.—First Admission: After the patient's temperature had been of the spiking type for four days, sulfathiazole therapy was started. His temperature began to fall, although it remained somewhat elevated for the following ten days. It then remained normal for a week, after which the administration of sulfathiazole was discontinued. At this time his temperature rose slightly for three days; then it dropped to normal and remained normal for two weeks. After this it became elevated again. With administration of sulfathiazole, the temperature fell to normal and remained normal for two weeks. Such courses continued throughout the patient's stay in the hospital, and the bouts of fever were controlled by sulfathiazole, which was last given on June 15, 1943. With the exception of a slight rise on two different occasions, his temperature remained normal until the date of discharge.

5. Basu, C. C.: Notes on a New Strain of Actinomyces Obtained by Blood Culture, Indian J. M. Research **25**:325-327, 1937.

The systolic murmur changed in character and intensity during the first three days. A diastolic murmur developed on the fourth day. This murmur was predominant for several weeks, after which it disappeared and only a rough systolic murmur remained.

Petechiae occurred in the conjunctivas on January 4. Several other petechiae occurred during the next few weeks, but after that time no more appeared during this hospitalization. The spleen was never palpated.

The patient gained weight and voiced no complaints except for occasional mention of painful spots on fingers and a heel. The tonsils were removed on March 3. At one time urinary suppression developed, after hematuria from sulfathiazole, but the condition improved with discontinuation of the drug. Leukopenia occurred on several occasions, but this disappeared with cessation of the drug.

All laboratory tests gave values within the normal range except for the weekly readings of the sedimentation rate, which was high up to May 6, 1943, when it became normal, and for leukopenia and hematuria associated with a drug reaction.

The patient was discharged on July 7, although he was not considered cured. At home he received sulfathiazole intermittently, to control the bouts of recurrent fever.

Second Admission: On November 1, the patient was admitted to Gorgas Hospital for a survey by the medical examining board. The blood pressure was 120 mm. of mercury systolic and 70 diastolic. No cardiac enlargement or arrhythmia was noted. A prolonged blowing systolic murmur was present over the entire precordium. The patient was again having bouts of fever, with his temperature rising to 102 F. He showed good response to sulfathiazole, 2. Gm. of which was given as an initial dose and 1 Gm. three times a day to attain a total of 69 Gm. in three different courses. The pulse rate varied between 70 and 118. The respiration remained normal.

Laboratory examination showed a rapid sedimentation rate on three different occasions (60, 60 and 90 mm. in one hour in the Westergren tube). The hemogram showed: 4,550,000 erythrocytes per cubic millimeter, 13.5 Gm. of hemoglobin (Sahli) per hundred cubic centimeters, a hematocrit reading of 40, a mean corpuscular volume of 87.9 cubic microns, a mean corpuscular hemoglobin value of 29.7 micromicrograms, a mean corpuscular hemoglobin concentration of 33.8 per cent, a color index of 0.873 and a volume index of 0.915. Two leukopenic counts, were reported (3,000 and 4,000 leukocytes per cubic millimeter). A fragility test showed beginning hemolysis in 0.44 per cent sodium chloride solution and complete hemolysis in 0.30 per cent solution. Two specimens of urine showed red cells on microscopic examination and were positive for albumin. One specimen showed finely granular casts. Several specimens revealed a few pus cells. Repeated blood cultures were sterile. An electrocardiogram showed right axis deviation and notching in the P wave in all leads. All other laboratory tests failed to give positive information.

At this time, December 14, the patient was discharged with the diagnosis of "valvular heart disease, mitral; subacute endocarditis, cause undetermined; blood cultures, sterile."

Third Admission: On March 4, 1944 the patient was readmitted to a Canal Zone hospital because sulfathiazole was having no further effect on the course of the disease. At this time the patient was well developed, though thin and pale, and appeared chronically ill. The blood pressure was 130 mm. of mercury systolic and 60 diastolic. He was not as alert mentally as previously, but he was conscious and oriented. A half dozen petechiae were found on the palms. Numerous petechiae were present in the conjunctivas. The lungs showed no

abnormality. The heart did not appear enlarged, and it had a slow rate and a regular rhythm. Harsh, rough systolic and early diastolic murmurs were distinctly audible over the apex. The rest of the physical examination showed nothing remarkable.

The hemoglobin was 60 per cent (Sahli) repeatedly. The erythrocyte count ranged between 3,000,000 and 4,000,000 per cubic millimeter. The leukocyte count ranged between 7,150 per cubic millimeter on the day of admission and 26,000 per cubic millimeter on March 20, 1944, with differential counts of 39 per cent polymorphonuclear leukocytes and 57 per cent lymphocytes, and 98 per cent polymorphonuclear leukocytes and 2 per cent lymphocytes, respectively. The urine repeatedly showed albumin (4 plus), casts (4 plus), around 20 pus cells per high power field, and many red cells. Of a total of 11 blood cultures, 6 were sterile and 5 were contaminated. The contaminants were in part possibly due to transportation of cultures on the train. The Kahn test was negative. The nonprotein nitrogen was 53.4 mg. per hundred cubic centimeters of blood. The sedimentation rate was 84 mm. in forty-five minutes. The spinal fluid was reported to have a normal sugar content, 2 plus protein, 204 cells per cubic millimeter. of which 95 per cent were lymphocytes and 5 per cent polymorphonuclear leukocytes, and a pressure of 270 mm. of water. Cultures were sterile.

During this last stay in the hospital the patient received 51 Gm. of sulfadiazine by mouth and ten separate doses of 50 cc. of a 2.5 per cent solution of sulfadiazine intravenously in nine days. Six transfusions of 250 cc. each were given. The heart murmurs were aggravated, and the number of petechiae increased greatly. The temperature ranged between 97.4 F. and 105.2 F. It showed a daily rise and drop, with the peak mostly around 103 F. and the low point around 99.0 F. The pulse rate was for the most part around 120, but it reached as high as 160 before death, on March 27, 1944.

Postmortem Diagnoses.—The following diagnoses were abstracted from the protocols and associated with more detailed elaboration in reference to the organs chiefly involved.

The anatomic diagnoses were: vegetations of the mitral valve, large, acute, ulcerative; acute focal myocarditis; endocardial wrinkling, extensive; myocardial. fibrosis; cardiac hypertrophy, 400 Gm.; pulmonary edema, bilateral; infarcts of the spleen with abscess formation; infarct of the ileum with abscess formation; infarcts of the kidneys; multiple punctate hemorrhages of the kidneys; acute and subacute focal glomerulonephritis, bilateral; acute and subacute pyelonephritis, bilateral; petechial hemorrhages of the conjunctivas, the buccal mucous membranes, the skin of the neck, extremities and trunk, the mucosal surfaces of the epiglottis, larynx and trachea, the pleurae, the parietal pericardium and the mucosal surface of the bladder; subarachnoid hemorrhages, diffuse; chronic passive congestion of the liver, early; icterus, slight; accessory spleen, attachment to tail of pancreas.

The microscopic diagnoses were consistent with the anatomic. In addition. hepatic and myocardial abscesses were diagnosed.

The cause of death was subacute bacterial endocarditis.

Smears, Blood Chemistry, Serologic Tests and Routine Cultures.—Smears from the vegetation of the heart revealed "gram-positive short-chained cocci." Blood chemistry showed, per hundred cubic centimeters of blood, 155.8 mg. of nonprotein nitrogen, 121.6 mg. of urea nitrogen, 8.3 mg. of creatinine and less than 30 mg. of glucose. Acid phosphatase was 5.7 units (King and Armstrong), and alkaline phosphatase was 18.9 units, per hundred cubic centimeters of serum. The Kahn test of the blood and the Wassermann test of the spinal fluid were negative. Cultures of blood and urine were sterile. Cultures of an abscess of the brain

were contaminated. Cultures of the spinal fluid showed Staphylococcus aureus (hemolytic), possibly a contaminant from the autopsy room. Cultures from the vegetation of the mitral valve are described later.

Gross Pathologic Observations.—The brain was swollen and edematous, with flattened gyri and shallow sulci. Numerous punctate hemorrhages were scattered through all. lobes, most prominent in the frontal lobes. Small hemorrhages were present in the basal ganglions. An area of softening, measuring 1.5 cm. in its greatest dimension, was located superficially in the right lateral occipital region. This area was hemorrhagic and contained a small amount of creamy yellow pus.

The heart (fig. 1 *A*) was slightly enlarged, weighing 400 Gm.. The apex lay opposite the fifth interspace, 9 cm. to the left of the midsternal line. The epicardium was smooth and glistening. There were several subepicardial petechiae. The myocardium was diffusely red-brown and firm. Here and there small, dark gray areas were present, indicating fibrosis. There was no evidence of infarction. The appearance of the chambers of the left side of the heart was greatly distorted by a vegetation which was attached to the auricular surface of the anterior cusp of the mitral valve. At its base the vegetation was firmly attached and occupied a region on the cusp measuring 3.5 cm. in the circumferential dimension and 1.0 to 2.5 cm. in width. It was soft and friable and extended into the chamber of the heart as a large fungating mass measuring 3.0 cm. in depth. At its base it was firm and gave the impression of long-standing attachment, but the peripheral parts were soft and friable and appeared to have been formed rapidly and recently. A small soft pinkish yellow vegetation, measuring 0.5 by 0.5 cm., was found on the posterior cusp of the mitral valve. The entire auricular surface of the mitral valve was swollen and moderately firm, but the tiny firm fibrous vegetations of rheumatism were not present. The chordae tendineae were not blunted. Extensive wrinkling was present in the endocardium of the left auricle, and the possibility of a rheumatic background for the valvular lesion was considered. The other valves were not affected. The circumferential valvular measurements were as follows: aortic valve, 6.5 cm.; mitral valve 10.0 cm.; tricuspid valve, 14.0 cm.; pulmonary valve, 6.5 cm. The left ventricular wall measured 2.1 cm., the right ventricular wall 0.6 cm. and the interventricular septum 2.0 cm. in thickness.

The kidneys (fig. 1 *A*) were similar in size and appearance, measuring 16 by 9 by 4.5 cm. The capsules stripped easily. The surfaces and the parenchyma of each kidney contained many punctate hemorrhages, so that they had a flea-bitten appearance. Several wedge-shaped firm grayish red infarcts were present in each kidney, and most of these contained irregular abscesses. The parenchyma was pale, grayish pink, soft and pliable. The cut edges everted; both kidneys were swollen and edematous. The corticomedullary boundaries were distinct. The calices and the pelves were not dilated, and the ureters were patent.

The entire gastrointestinal tract showed numerous small punctate hemorrhages. A reddish gray submucosal abscess, measuring 1.3 cm. in its greatest dimension, was located in the distal portion of the ileum.

The greater portion of the spleen (fig. 1 *A*) was friable and of a red-brown color. Approximately the lateral one half of the organ showed an area of irregular outline, firm consistency and gray-pink color, consistent with an old infarct, in which were several small pus pockets.

Microscopic Observations.—(*a*) Brain (fig. 4 *B, C* and *D*): A section taken from the right frontal lobe and stained with hematoxylin and eosin showed generalized areas of mild necrosis, evidenced by the variable amount of loss of distinctness of cytologic outline. One area extending into the cortex from the periphery of the section showed an eosinophilic amorphous coagulum.

A section taken from the lower portion of the right occipital lobe showed a thickening of the leptomeninges with areas of diffuse hemorrhage associated with diffuse cellular infiltration in which polymorphonuclear leukocytes, fewer lymphocytes and some macrophages participated, a few of the last-named being laden with a deep golden pigment. Fibrin was scattered throughout, evidenced by
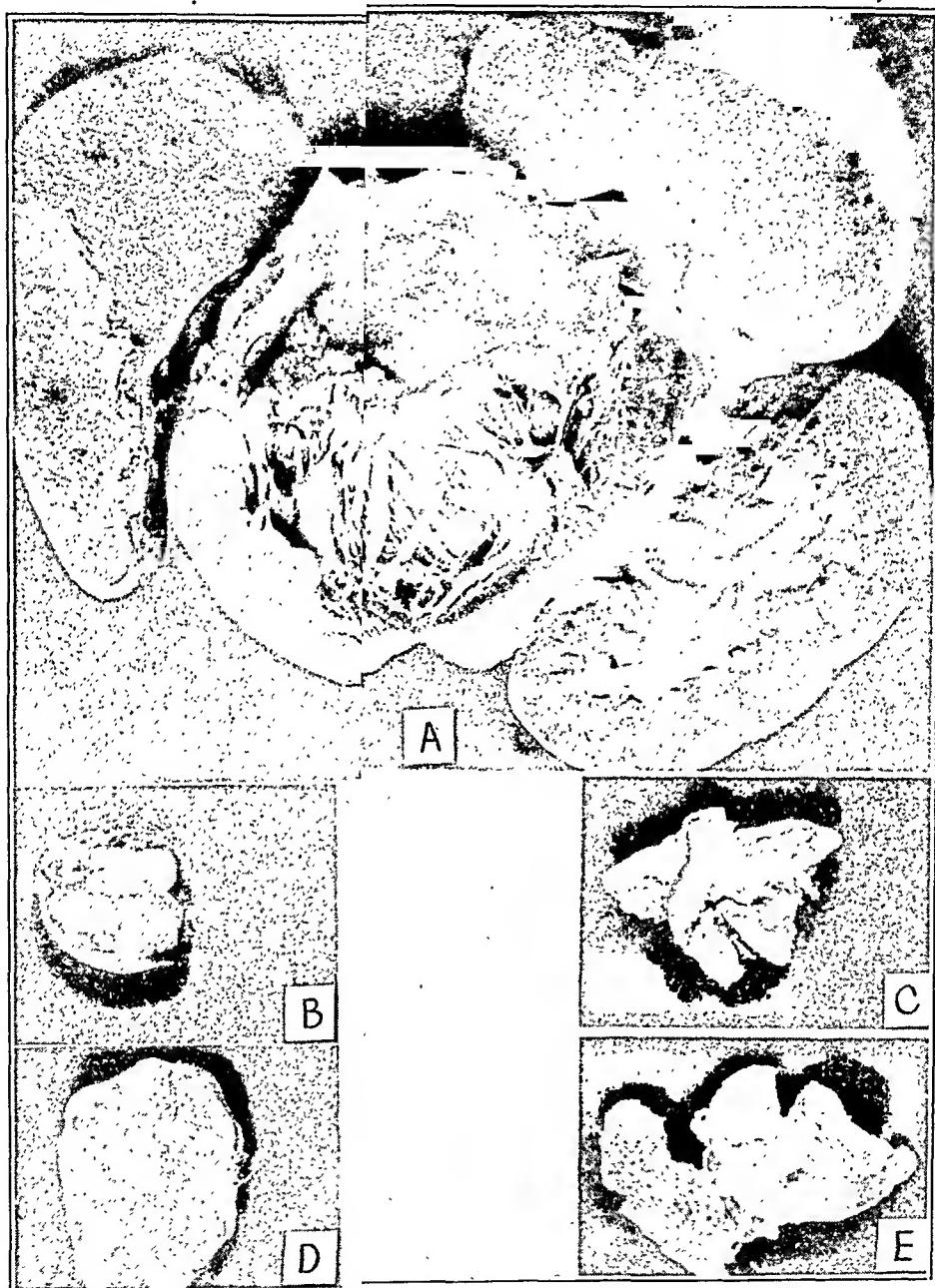
Fig. 1 (case 1).—*A*, gross autopsy specimens: the heart, the kidneys and the spleen. Note the vegetations on the mitral valve.

B and *C*, lymph node and lung, respectively, or a rat inoculated with a culture from the involved valve.

D and *E*, lymph node and lung, respectively, of a rat inoculated with Actinomyces grown from a sulfur granule in another case.[6]

eosin-staining strands. Mild fibroblastic proliferation was present through various areas. The inflammatory reaction was most marked in the perivascular areas. There were focal areas of microscopic abscesses in the cortical tissue, evidenced by aggregations of cells, predominantly polymorphonuclear cells, with a few lymphocytes and macrophages. Some of these abscesses were definitely perivascular, with the small vessels intact. Other areas in the section showed degenerative changes of the vessel wall, evidenced by eosinophilic foci of hyalinization. Some fields showed variable amounts of fibrin in the perivascular areas. One vessel showed complete occlusion of its lumen by basophilic cocci, cocci in chains, and rods (fig. 4 B). There was a mild perivascular infiltration of polymorphonuclear leukocytes, lymphocytes and macrophages in this region. The first mentioned cells predominated. Some of the other abscesses showed an occasional basophilic rod. Gram's stain (MacCallum's modification of Goodpasture's method) of the section showed the coccal structures and the rods to take a purple stain, and they were less distinctly observed with this stain.

A section taken from the occipital abscess and stained with hematoxylin and eosin showed extensive areas of cortical necrosis, hemorrhage and abscess formation, illustrated by the loss of outline of structural detail of cortical tissue and blood vessels in these areas, together with eosinophilic zones of hyalinization. Some of these areas were also associated with hemorrhage, presence of fibrin and extensively diffuse cellular infiltration, predominantly polymorphonuclear leukocytes together with some lymphocytes and macrophages, some of which were laden with a deep golden brown pigment. Focal clumps of basophilic cocci, cocci in chains, and rods were seen scattered through the collection of polymorphonuclear cells. Gram's stain showed these clumps of cocci and rods to take both a purple and a basophilic stain in this section.

(b) Heart: A section of the mitral valve (fig. 2 A) stained with hematoxylin and eosin showed an eosinophilic border of variable width, which was focally and diffusely infiltrated with basophilic clumps and clusters that assumed a variable pattern under low magnification. These patterns will be described in detail subsequently. The basophilic masses extended into the border and toward the base of the lesion: Areas of focal and diffuse cellular infiltration, polymorphonuclear leukocytes together with fewer monocytes, were also present in the border. These cells showed degenerative changes, observed in the loss of distinctness of structural outline. The outer border was covered in areas by focal and mildly diffuse infiltrations of degenerated polymorphonuclear leukocytes and fewer monocytes, together with fine eosinophilic fibers in some parts. The free border also showed areas of breaks of continuity of outline exposing the basophilic groups of clumps and clusters.

The connective tissue stroma adjacent to the border described showed areas of focal and diffuse abscess formation, evidenced by collections predominantly of polymorphonuclear leukocytes and fewer monocytes with basophilic vesicular nuclei and eosinophilic cytoplasm. Several of these cells were degenerated. A definite fibroblastic proliferation, together with the described inflammatory reaction, was present in the connective tissue stroma, which also showed fatty ingrowth in other areas, particularly around the blood vessels. The adjacent cardiac muscle bundles revealed nothing remarkable, but the supportive connective tissue stroma of these fasciculi showed areas of mild focal infiltration, polymorphonuclear leukocytes in association with a few monocytes with basophilic vesicular nuclei and eosinophilic cytoplasm.

Scrutiny of the valve section stained with hematoxylin and eosin with the oil immersion objective of the microscope (fig. 2 C, D, E and F) showed the afore-
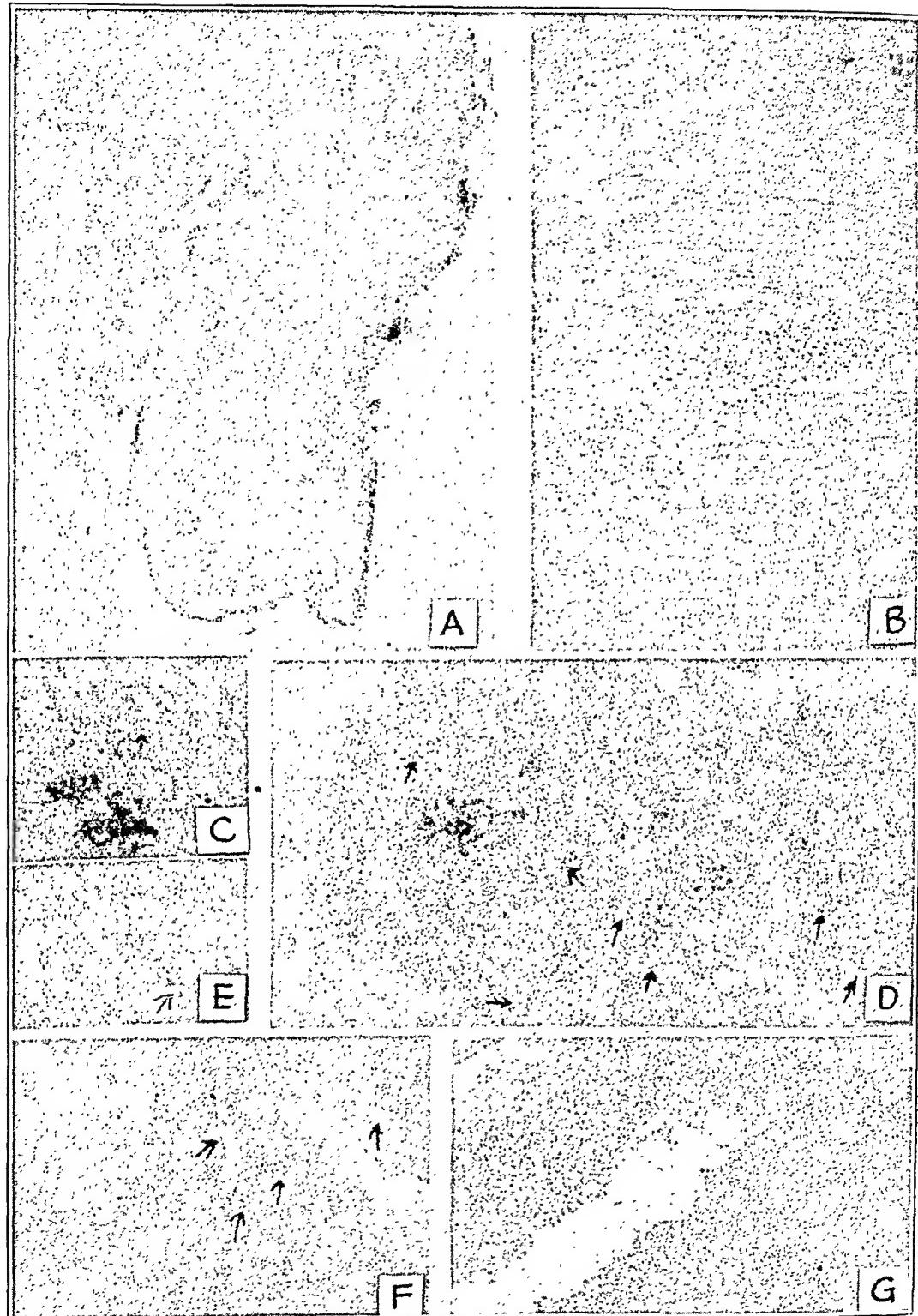
Fig. 2 (case 1).—*A*, section of the involved mitral valve (hematoxylin and eosin stain; × 75).

B, papillary muscle of the heart showing an abscess (hematoxylin and eosin stain; × 75).

C, D, E and *F*, various areas of the valve seen in *A*, under higher magnification, showing cocci, cocci in small chains, coccobacilli and rods (hematoxylin and eosin stain; × 950).

G, pleural exudate of a rat inoculated with a culture of Actinomyces from the

mentioned basophilic clumps and clusters to consist of basophilic cocci, diplococci, streptococci, rods, occasional clavate forms and short filaments, an occasional one of which showed small branches. This branching form was infrequent and difficult to demonstrate. Some of the rods were beaded and assumed the appearance of diphtheroids.. Others stained solidly. A few showed bipolar staining. Many of the rods were small and appeared similar to coccobacilli in structure. The predominating structures were the rods and the coccobacillary forms. Gram's stain showed the structures described as micro-organisms to be gram-variable. This stain showed that some of the rods were gram-negative with gram-positive poles.

Section of the myocardium showed areas of mild focal inflammatory reaction in the connective tissue stroma, observed by the presence of predominantly polymorphonuclear leukocytes and a few lymphocytes and macrophages, particularly in the perivascular areas. There was a moderate increase of epicardial fat. The arteries showed mild to moderate thickening of the intima. Section of a papillary muscle showed focal areas of microscopic abscesses in the connective tissue stroma (fig. 2 *B*).

(*c*) Spleen (fig. 3 *B*): A section of the spleen stained with hematoxylin and eosin showed an old infarct, evidenced by the ghostlike appearance of the entire section, which · revealed indistinctness of outline of the entire splenic structure associated with old areas of hemorrhage and necrosis. In these areas an indistinct appearance of trabeculae, central arteries, veins and red and white pulp was noted. The white pulp was markedly decreased, and none of the scattered lymphoid nodule–like structures showed germinal centers. Some of the central arteries were completely occluded by basophilic clumps of cocci, rods, and short and thin filaments in an amorphous eosinophilic substance. Many of the perivascular areas were diffusely infiltrated, predominantly by degenerated polymorphonuclear leukocytes. Several of these cells extended into the adjacent pulp for a variable distance. The capsule showed loss of distinctness of outline to a variable degree.

(*d*) Liver (fig. 3 *C*): A section stained with hematoxylin and eosin showed a moderate increase of lymphocytic infiltration in the portal areas. The sinusoids were dilated, and many of them were mildly infiltrated, by polymorphonuclear leukocytes and a few lymphocytes, extending through the lobules. Occasional microscopic abscesses were present in the central areas of the lobules.

(*e*) Intestine (fig. 3 *D*): A section stained with hematoxylin and eosin showed extensive areas of necrosis, hemorrhage and abscess formation through all layers of the segment of small intestine. Some segments were entirely denuded of mucosal surface. Some of the blood vessels showed necrotic walls and an eosinophilic and hyalinized content within their lumens, associated with cellular debris, which occluded some of the lumens. Other lumens seemed almost occluded by basophilic clumps of cocci, streptococci and rods, already described. These structures were also seen in clumps in the eosinophilic masses among the numerous polymorphonulear leukocytes in the adjacent abscess.

(*f*) Kidneys (fig. 3 *E*): A section stained with hematoxylin and eosin showed degenerative changes in several glomeruli, observed in the hyalinization of a variable portion of the glomerular tuft, particularly at the base. Some of Bowman's capsules showed mild inclusions of polymorphonuclear leukocytes. Some of the lumens of the tubules showed inclusions of macrophages laden with a deep yellow pigment. Many of the collecting tubules contained numerous erythrocytes. There were focal and mildly diffuse inflammatory changes in the parenchyma with presence of predominant polymorphonuclear leukocytes and fewer lymphocytes, macrophages and plasma cells. Many small parenchymal hemorrhages were present. An infarct of moderate size was also seen. A small area showed ·pyelone-
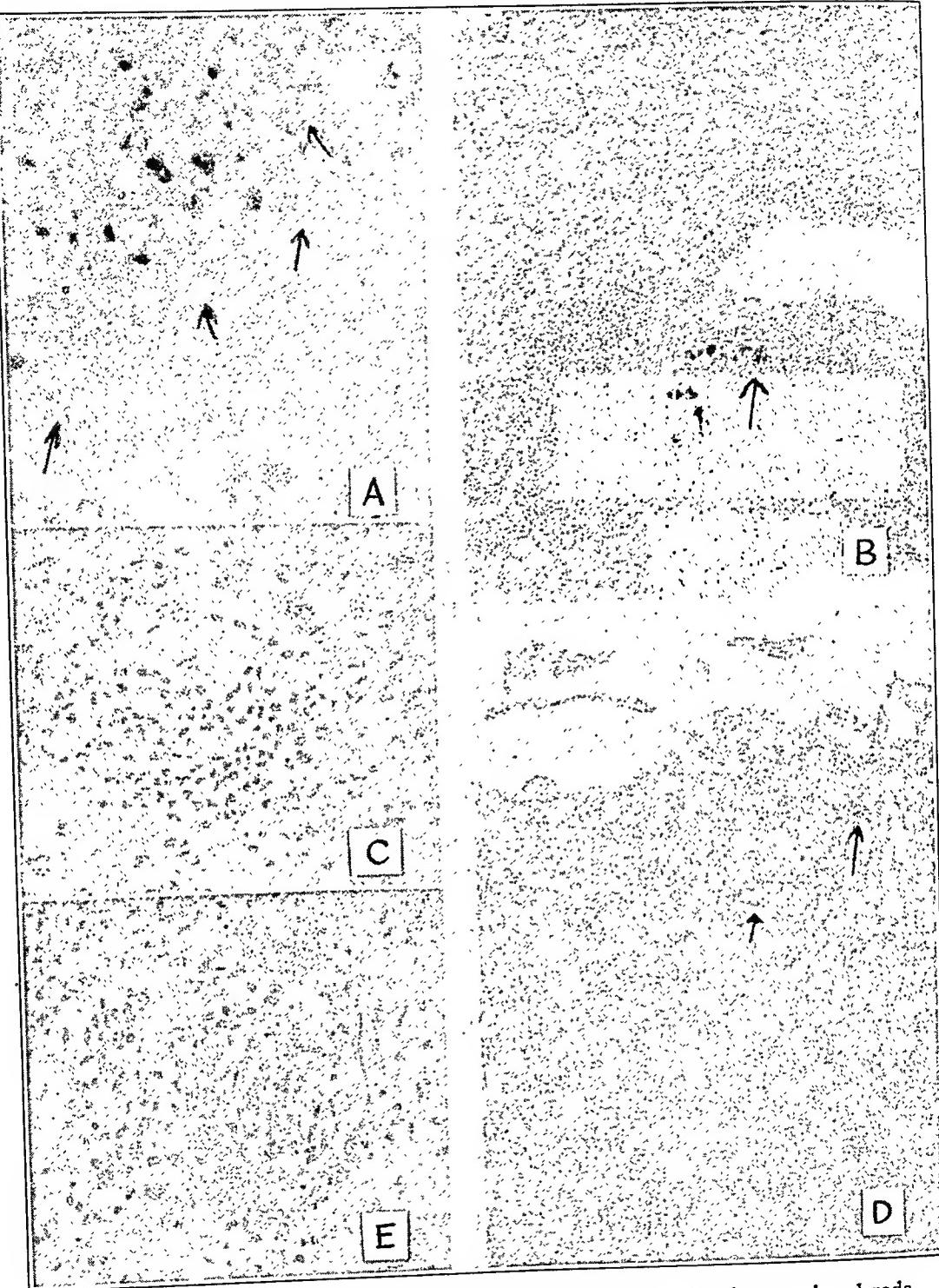
Fig. 3 (case 1).—*A*, higher magnification of figure 2 *G*, showing cocci and rods (hematoxylin and eosin stain; × 950).
B, spleen showing occluded blood vessels (hematoxylin and eosin stain; × 100).
C, liver showing a microscopic abscess (hematoxylin and eosin stain; × 400).
D, small intestine showing necrosis of tissue and occluded vascular lumens (hematoxylin and eosin stain; × 75).
E, renal glomerulus showing degenerative changes (hematoxylin and eosin stain; × 400).

phritic changes, evidenced by areas of hyalinization together with mild lymphocytic infiltration in the connective tissue stroma.

Cultures of the Mitral Valve.—A large segment of the growth of the mitral valve was washed several times in sterile isotonic solution of sodium chloride. It was then placed in a sterile Petri dish and seared over the entire external surface with a red hot spatula. At this stage it was removed to a second sterile Petri dish, where the seared tissue was cut with a sterile scalpel. Fragments from the inner surfaces of the cut tissue were cultured aerobically, under reduced oxygen tension and under carbon dioxide tension, on several blood slants (10 and 33 per cent whole blood with 2 per cent dextrose agar base), on dextrose agar slants, on plain agar and in "hormone" broth,[5a] all at 37 C. All inoculated mediums left in the incubator aerobically and under reduced oxygen tension remained sterile. Only the blood slants and the "hormone" broth incubated under carbon dioxide tension showed growth. This growth was slow. Cultures were studied from growth of single colonies. The blood slants showed small pinpoint colonies in five days. These were gray-brown, soft in consistency and easily removed from the slant. Subsequently, the colonies became somewhat larger, their diameter increasing to as much as 0.2 cm. The color remained the same, but the consistency became firmer. Transfers were made every week. After thirty-five days the colonies had died; further subcultures showed no growth.

In "hormone" broth, small soft gray granule-like colonies were visible in a week. These were transferred to blood plates and developed the characteristics described in the foregoing paragraph. Colonies transferred from blood plates to dextrose agar grew with difficulty under carbon dioxide tension.

Microscopically, the five days' cultural growth (fig. 4 *E*) showed gram-variable cocci, diplococci, streptococci, rods and diplobacilli of variable size and shapes. On dextrose agar a fourteen day old growth showed gram-variable cocci and rods, some of which measured up to about 0.7 micron in width. Some rods were long and straight; others were clavate. These structures took a basophilic stain with Giemsa's method. On blood slants the sixteen day old growth (figs. 4 *F, G* and 1) showed gram-variable cocci, diplococci, streptococci, rods and a few filaments, some of which showed septums and occasional ones branching forms. The predominating form was the rod. These structures took a basophilic stain with Giemsa's method. Many of these rods presented a morphologic similarity to those observed in the tissue section of the mitral valve. The twenty-six day old growth showed cocci, diplococci, streptococci, rods, diplobacilli, beaded rods, clavate forms and filaments, some of which showed septums and a few of which showed short rami. Occasional forms showed delicate mycelia, with septums and rami, extending from an oval body (fig. 4 *H*). These filaments measured up to about 0.5 micron in width. The hematoxylin and eosin stain showed these structures to be both basophilic and eosinophilic. The twenty-eight days' growth showed several branching filaments in the direct unstained preparation in isotonic solution of sodium

5a. "Hormone" broth is made up as follows: Step 1. Add lean ground beef or veal, 500 Gm., to distilled water, 1,000 cc., and heat until mixture just begins to boil; then place in bath at 56 C. for one hour, after which filter the mixture through gauze and a thin layer of cotton. (The filtering through gauze and cotton permits enrichment of the medium.)

Step 2. Add: proteose peptone, 10 Gm., sodium chloride, 5 Gm.; disodium phosphate, 2 Gm.; sodium citrate, 2 Gm.; Bacto-dextrose, 1 Gm.; agar, 1.5 Gm.; Bacto-gelatin, 10 Gm. Mix and heat until agar dissolves. (Do not allow it to boil more than thirty-seconds.) Restore volume to 1,000 cc. Titrate to p_H 7.4. Bottle and sterilize at 15 pounds (6.5 Kg.) for twenty minutes.
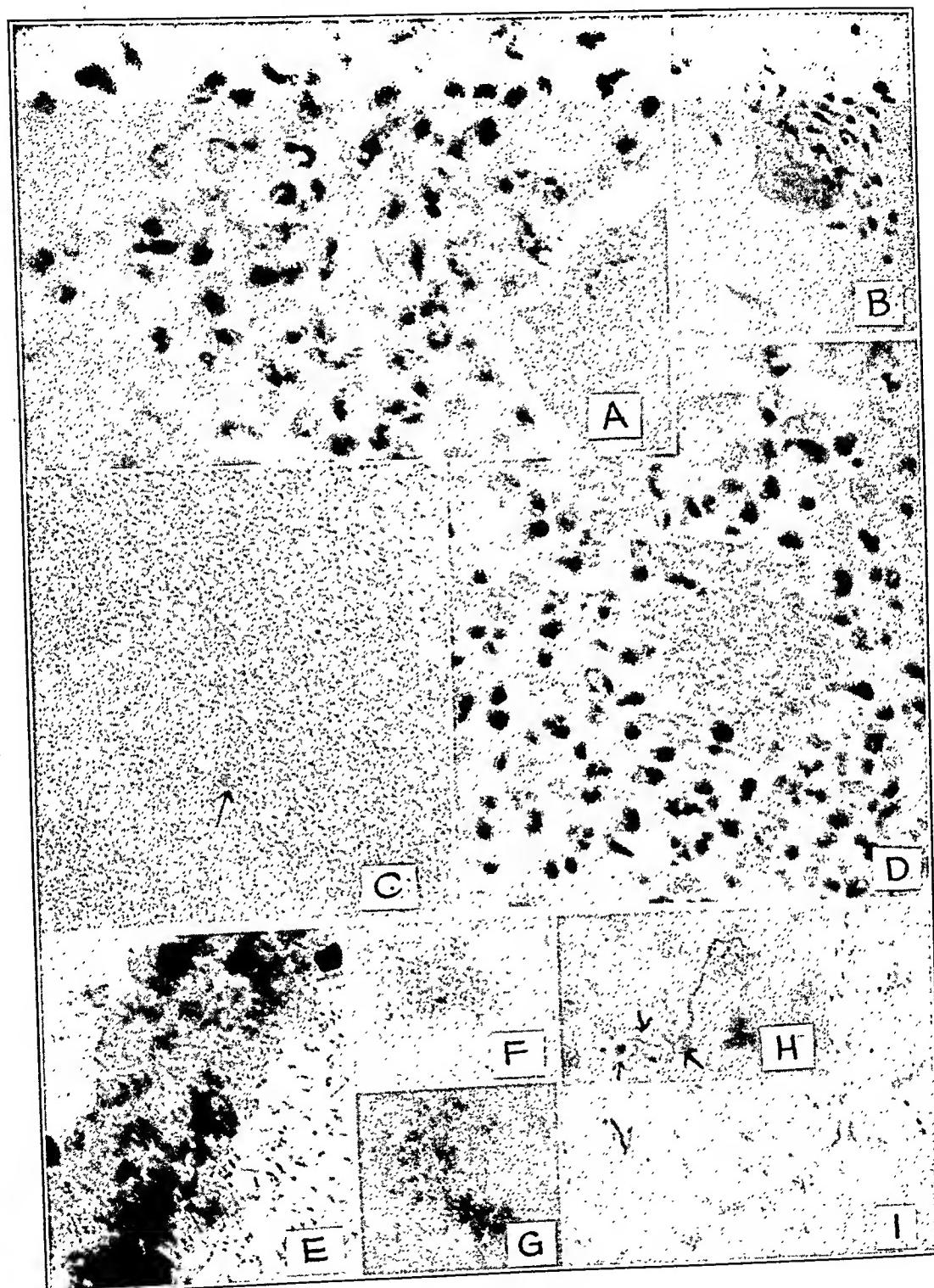
Figure 4
(See legends on opposite page)

chloride (fig. 5 *A*). The hematoxylin and eosin stain of the thirty-three days' growth showed degenerated eosinophilic rods and a few basophilic filaments. An occasional basophilic filament showed septums, fusiform enlargement and a chlamydospore (fig. 5 *B*).

ANIMAL INOCULATION IN CASE 1.—On April 5, 1944 a white rat was inoculated intraperitoneally with an eight days' growth from a culture of the vegetation of the mitral valve on a blood slant. The rat died July 8, ninety-four days after inoculation, and autopsy was performed shortly after death, according to the technic described subsequently. The animal was emaciated. There were extensive pathologic changes in both lungs, with marked fibrinous exudation (fig. 1 *C*) over pleural surfaces bilaterally. Both the lungs and the mediastinum showed multiple abscesses with a glairy and mucoid exudation of a green-yellow color. Other abscesses showed a finely granular substance, but no true sulfur granules were present. The upper lobe of the right lung showed a finely granular structure of firm consistency and a gray-red color. A mesenteric nodule (fig. 1 *B*), measuring about 2 cm. at the largest dimension, was smooth, firm and of a gray color. On sectioning, the surfaces showed a hemorrhagic spot measuring up to about 0.6 cm. at the largest dimension. The remaining portions of the surfaces made by sectioning were mottled with gray and red-brown colors.

Microscopic Observations.—(*a*) Lung: Sections stained with hematoxylin and eosin showed chronic peribronchial and peribronchiolar inflammatory changes. There were also focal areas of bronchopneumonia, atelectasis, congestion and hemorrhage. One arteriole in particular showed splitting of the internal and the external elastic lamella and marked thickening of the media with zones of fatty ingrowth. Adjacent to the external elastic lamella were eosinophilic zones of hyalinization.

Pleural surfaces showed extensive acute purulent inflammatory changes (figs. 2 *G* and 5 *C*), evidenced by diffuse cellular infiltration, predominantly polymorphonuclear leukocytes, with several lymphocytes and some macrophages. Many of these cells showed necrosis. Fibrous strands of eosinophilic staining were present among these cells in various areas. Numerous basophilic cocci, cocci in chains and a few rods and diplobacilli were scattered among the inflammatory cells. Some of the described inflammatory cells extended into the adjacent pulmonary parenchyma. Many of the described micro-organisms (fig. 3 *A*) showed

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EXPLANATION OF PLATE.

Fig. 4 (case 1).—*A*, kidney showing interstitial inflammatory reaction (hematoxylin and eosin stain; × 950).

B, brain showing blood vessel occluded by micro-organisms and perivascular inflammation (hematoxylin and eosin stain; × 400).

C, brain showing a focus of micro-organisms circumscribed by inflammatory cells (hematoxylin and eosin stain; × 950).

D, brain showing a focus of micro-organisms (hematoxylin and eosin stain; × 75).

E, culture of the involved mitral valve showing five day old growth (Gram's stain; × 950).

F, *G* and *I*, culture of the mitral valve showing variations of forms in a sixteen day old growth (Giemsa's stain; × 950).

H, culture of the mitral valve showing a branching form in a twenty-six day old growth (hematoxylin and eosin stain; × 950).
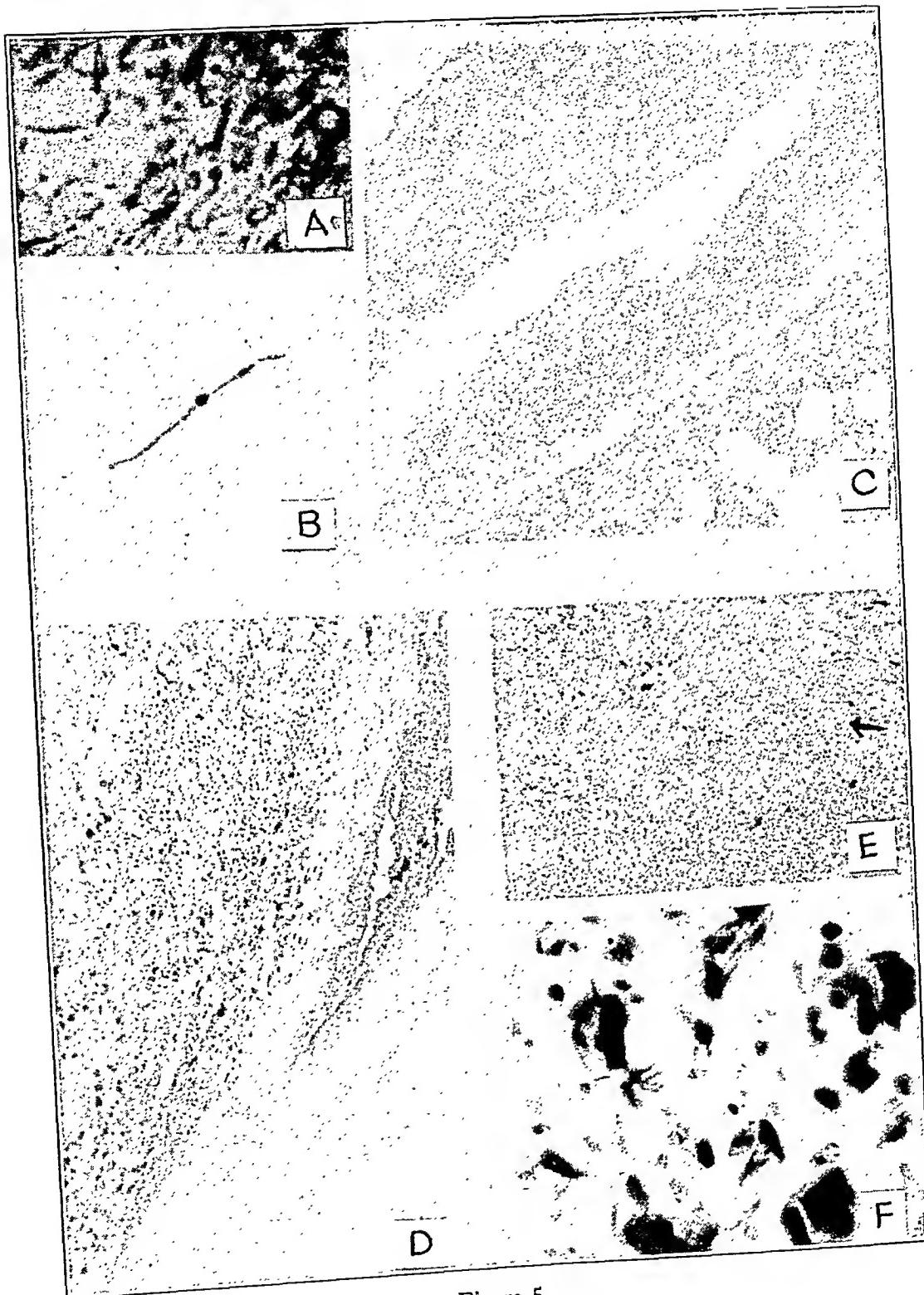
Figure 5
(See legends on opposite page)

morphologic and staining characteristics similar to those observed in the heart valve of the patient. Occasional basophilic clumps of cocci and cocci in chains were present among the inflammatory cells in the pulmonary parenchyma.

(*b*) Lymph Node: A section (fig. 5 *D*) taken from the node already described in the gross and stained with hematoxylin and eosin showed areas of necrosis involving large segments of the capsule and extending for a short distance in the adjacent parenchyma, illustrated by the ghostlike appearance of these structures. Other segments of the capsule and large areas of the node showed only mild loss of distinctness of outline of cellular detail. The capsule was thickened. The subcapsular sinus was not recognized. The detailed normal structure of the lymph node had been lost. Focal areas of lymphocytic aggregation were present about the peripheral portion of the node, and fewer of these showed portions of recognizable germinal centers. Extensive areas of hemorrhage were present in the node. Connective tissue trabeculae were recognized as extending from the capsule. There were extensive and diffuse infiltrations of large round and polyhedral mononuclear cells with basophilic round vesicular nuclei, centrally and eccentrically located. Some large cells had two nuclei, and others had several. There were some areas diffusely infiltrated by similar cells associated with several polymorphonuclear leukocytes. This combination of cells was not predominant, however. Some areas showed marked fibroblastic proliferation, particularly in the perivascular areas, in which regions some basophilic rods and diplobacillary forms were present (fig. 6 *A*, *B* and *C*). Other areas showed fibroblastic proliferation in a loose connective tissue stroma associated with an amorphous eosinophilic coagulum and scattered macrophages and lymphocytes. Some of the vessels showed mild intimal thickening and narrowing of their lumens. In addition to the aforementioned findings, there were numerous crystals (fig. 5 *F*) of rectangular, square and slightly fusiform shapes and of eosinophilic staining. Some of these crystals were homogeneous and others appeared longitudinally striated. Some were extracellular, and others were within the cytoplasm of the large mononuclear cells. These crystals at times assumed the shape of portions of an asteroid, but true asteroids were not found. The crystals were gram-variable with MacCallum's modification of the Gram stain. The entire picture of the lymph node was consistent with a process of chronic inflammation and lymphoid hyperplasia with subsequent pressure necrosis of tissue due to impairment of blood supply. Particular attention should be given to the description of the bacillary structures in the node, since similar

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EXPLANATION OF PLATE.

Fig. 5 (case 1).—*A*, culture of the mitral valve showing branching filamentous forms in twenty-eight day old growth (direct and unstained preparation; × 950).

B, culture of the mitral valve showing a chlamydospore in a thirty-three day old growth (hematoxylin and eosin stain; × 950).

C, lung and pleural surface of a rat inoculated with a culture of the mitral valve (hematoxylin and eosin stain; × 75). See also figures 2 *G* and 3 *A*.

D, lymph node of a rat inoculated with a culture of the mitral valve (hematoxylin and eosin stain; × 75). See also figure 1 *B*.

E, same as *D*. The arrow points to the locality of the rod structures indicated in figure 6 *A*, *B*, and *C*.

F, crystals observed in the lymph node shown in *D* (Gram's stain, MacCallum's modification of Goodpasture's method; × 950).
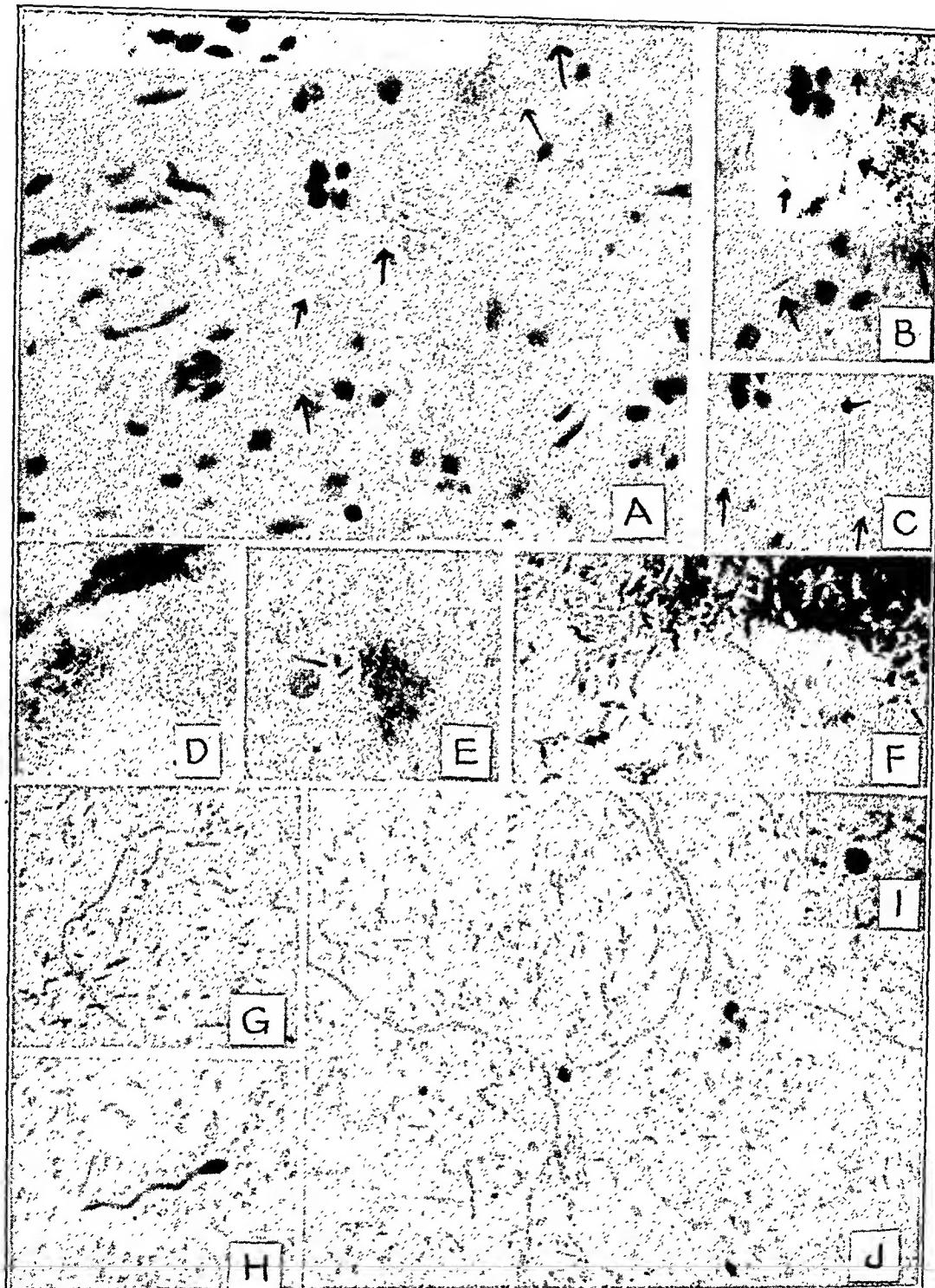
Fig. 6 (case 1).—*A*, *B* and *C*, lymph node shown in figure 5 *E*. Arrows point to bacillary structures in the fibrous connective tissue stroma of the perivascular area (hematoxylin and eosin stain; × 950).

D, *E*, *F* and *G*, coccal, bacillary and filamentous forms as seen in seventy-two hours' growth of cultures of pulmonary abscesses and pleural exudate of a rat inoculated with a culture of the mitral valve (Gram's stain; × 950).

H, *I* and *J*, twenty-one days' cultural growth of the micro-organism in *D* (Gram's stain; × 950).

structures were seen in a lymph node (fig. 1 *D*) from another rat inoculated with cultures from true "sulfur granules" of another patient.[6]

Culture from Inoculated Animal.[7]—The rat was immersed in solution of formaldehyde U.S.P. diluted 1 : 10, to kill external contaminants. The body cavities of the animal were opened with an aseptic technic. Pulmonary abscesses and pleural exudate of the rat were cultured in the manner described on page 215 under "Cultures of the Mitral Valve." In gross appearance the colonies were similar to those isolated from the patient's heart valve, but they developed more rapidly. In three days they were of about the same size as those observed at five days in cultures of the patient's mitral valve. These organisms, like those of the patient's heart valve, grew only under carbon dioxide tension.

Microscopically, the seventy-two hour growth showed gram-variable cocci, diplococci, rods and some filaments (fig. 6 *D, E, F* and *G*), some which showed septums. Occasional branching forms were present. A few round and baglike structures (fig. 6 *I*), measuring from about 3 to 4 microns in diameter, were also seen. These bags contained numerous small granules, and they will be mentioned again in connection with other strains of Actinomyces in another paper.[6] Some of the rods present resembled diphtheroids. The twenty-one day cultural growth showed gram-variable rods and filaments, some of which had septums and branching forms. Filaments sprouting from oval bodies (fig. 6 *H*) and chlamydospores (fig. 6 *J*) were present in this culture. The round bags aforementioned were also present. Transfers from this stage showed no growth.

CASE 2.—This case came to my attention while the preparation of this paper was in progress.

Clinical History.—A 71 year old Jamaican Negro woman, a housewife, died in Panama City, Republic of Panamá, Nov. 17, 1945. The body was brought to the Board of Health Laboratory, Ançon, Canal Zone. A death certificate accompanying the body gave the cause as "cardiorenal" disease. The attending physician informed me that he had seen the patient off and on for several years and that during this time she had presented the syndrome of typical hypertensive heart disease with damage of the kidneys. She had high blood pressure and presented evidence of cardiac decompensation on occasions. She had never shown, to his knowledge, any evidence of rheumatic heart disease or any symptoms of subacute bacterial endocarditis. No petechiae had been found. The husband said she had been confined to bed at home for the last two months before her death.

Autopsy.—The heart was enlarged and weighed 470 Gm. There was particularly evident preponderance of the left ventricle. The pericardial sac contained 30 cc. of straw-colored fluid. The endocardium of the left auricle was wrinkled in various areas. Fine fibrotic nodules were present in the aortic and the mitral

6. Wedding, E. S.: Actinomycosis of the Central Nervous System and Its Coverings, Primary and Secondary Forms: Report of Seven Cases and Review of Literature, unpublished data.

7. A culture of the micro-organism isolated from this animal was inoculated into a second rat, which was killed eighteen months after inoculation. Although the later rat looked entirely healthy prior to death, it presented several large mesenteric lymph nodes quite similar in their gross and microscopic pathologic aspects to the lymph node described in the first rat except for the absence of any forms of the micro-organism and crystals in histologic preparations.

leaflets, consistent with inactive rheumatic heart disease. The nodules of the aortic cusps presented superficial growths of a verrucous structure, which were friable. The left aortic leaflet was ruptured. The right posterior aortic leaflet was bound to the anterior one. An area of fibrosis was evident in the endocardium of the left ventricle.

Microscopic examination of a section of the aortic valve, taken through a region of the verrucous growth, showed diffuse acute inflammatory changes through the greater portion of the section, indicated by the cellular infiltration, predominantly polymorphonuclear leukocytes with a few lymphocytes and macrophages. In various areas, diffuse fibroblastic proliferation was present, particularly toward the base. Regions of the valvular border showed breaks in continuity of outline. These regions were associated with the inflammatory cells described, which covered the adjacent borders and were in line of direct contact with the inflammatory cells which extended throughout the entire thickness of the section. At the base the inflammatory cells extended into the adjacent fibrous connective tissue stroma supporting the myocardial fasciculi. Various areas adjacent to the border showed necrosis of tissue. Focal areas of calcific changes were present in the border of the valve, near some of which focal collections of basophilic structures were observed, with the oil immersion objective of the microscope, to consist of basophilic cocci, coccobacilli, rods and long, thin filaments. Some of these structures stained lightly, and others stained deeply. Adjacent regions were diffusely infiltrated by basophilic cocci, coccobacilli, rods and a few short filaments among the inflammatory cells. Some of the filaments were septate, revealed by Gram's stain. This stain showed structures similar to those described to be gram-positive. Clavate forms were also present. A few of the rods were gram-negative.

A direct smear prepared from the vegetations of the valve and stained by Gram's method showed structures the same as those already described except that no branching forms were observed.

Cultures were made from the cardiac vegetations, and an aerobic strain of Actinomyces was recovered in twenty-four hours, in which stage the structures occurred as cocci, rods and filaments. The colonies were gray-white and showed branching filaments after eight days. These stained gram-variable. Unfortunately, an adequate bacteriologic technic was not carried out, and the organism was not recovered in pure culture from the start, although separate colonies of Actinomyces were singled out and grown in pure culture from this stage. No animals were inoculated.

Laboratory reports on an autopsy blood specimen showed 183.9 mg. of nonprotein nitrogen, 149.6 mg. of urea nitrogen, 12.5 mg. of creatinine and 30 mg. of glucose per hundred cubic centimeters. The Wassermann and the Kahn test of the blood were negative.

COMMENT

A vast amount of literature has been written on the subject of actinomycosis. Yet it is surprising how many physicians think of this diseasse in terms of the "sulfur granule" only. I believe that it is entirely proper to emphasize the established facts that the granule is not a true criterion for the diagnosis of actinomycosis, that other organisms may produce granules and that some species of Actinomyces do not form clubs. Numerous strains of Actinomyces have been reported, both

as pathogens and as saprophytes (Bergey[8]; Dodge[9]; Topley and Wilson[10]). Classifications have been discussed and disputed. Pathogens have been described as anaerobic, microaerophilic and aerobic. Some strains have been mentioned as acid fast. Emmons[11] has clarified and simplified the understanding of actinomycosis by defining the disease as "an infection caused by invasion of the host by some species of Actinomyces." He refers to Bergey and Topley and Wilson as authority for his usage. By keeping such a definition in mind and by understanding the pleomorphic cultural characteristics of Actinomyces, which occurs as cocci, rods, filaments, branching filaments, irregular vesicles and diphtheroid forms (Emmons[11]; Naeslund[12]; Kessel[13]; Negroni[14]) it is probable that greater care will be used in the laboratory to recover the organism. Such an organism recovered by competent personnel would then be less apt to be considered a contaminant and discarded on this ground, which would be the easiest way out of doing a job.

It is of interest to read how Naeslund[12] referred to the pleomorphism: "There are hardly any known bacteria that exhibit such large variations from a cultural point of view as Actinomyces." Novak and Henrici,[15] and Sartory and Meyer[16] made references to a filtrable form of Actinomyces. I[6] have recovered a filtrable form repeatedly in cultures of one of my strains of Actinomyces.

In this paper the emphasis of the review of the literature has been confined to those cases in which evidence of endocarditis was presented without any evidence of a portal of entry. The organism reported by Jervell was classified as a leptothrix by him, and it is not to be considered as a strain of Actinomyces. The organism recovered from the blood stream in the first case of Alestra and Girolami developed into

8. Bergey, D. H.: Bergey's Manual of Determinative Bacteriology, ed. 5, Baltimore, Williams & Wilkins Company, 1939, p. 839.

9. Dodge, C. W.: Medical Mycology, St. Louis, C. V. Mosby Company, 1935, p. 705.

10. Topley, W. W. C., and Wilson, G. S.: Principles of Bacteriology and Immunity, ed. 2, Baltimore, William Wood & Company, 1937, p. 263.

11. Emmons, C. W.: Actinomyces and Actinomycosis, Puerto Rico J. Pub. Health & Trop. Med. **11**:63-76, 1935.

12. Naeslund, C.: Studies of Actinomyces from the Oral Cavity, Acta path. et microbiol. Scandinav. **2**:110-140, 1925.

13. Kessel, J. F., and Goolden, E. B.: A Comparison of Strains of Actinomyces Recovered from Human Lesions, Am. J. Trop. Med. **18**:689-701, 1938.

14. Negroni, P.: Actinomicosis humanas producidas por agentes anaerobios, Rev. argent. de dermatosif. **18**:24-27, 1934.

15. Novak, M. V., and Henrici, A. T.: Pleomorphic Organisms Showing Relationships Between Staphylococci and Actinomycetes, J. Infect. Dis. **52**:253-267, 1933.

16. Sartory, A.; Sartory, R., and Meyer, J.: Sur les propriétés ultrafiltrantes de l' "Actinomyces bovis" Harz à travers les sacs de collodion implantés dans le péritoine du cobaye, Bull. Acad. de méd., Paris **110**:797-798, 1933.

filaments, but no branched forms occurred. Since the authors reported that the strain was lost in an early stage of development, it is not possible to classify it either as a leptothrix or as strain of Actinomyces. The strain recovered from the blood stream in the second case developed into filaments, but branching forms are not mentioned. For this reason, it cannot be regarded as a species of Actinomyces, although the authors believed they were dealing with "Nocardia." Cornell and Shookhoff[1] referred to the case of Lutz (table 3) with regard to a primary cardiac involvement with multiple small abscesses in the wall of the right ventricle, but the details are not complete. The organism described by Basu[5] developed branching forms, but the author does not mention cardiac involvement. Carrión[17] reported the recovery of positive rods and branching filaments from a blood culture in case 2, but there is no reference to cardiac lesions. Freed[18] reported blood cultures positive for Actinomyces, but there was no clinical evidence of cardiac impairment, although the endocardium of the right ventricle was perforated by the abscess. Bruun[19] referred to Schlegel's case of actinomycotic pyemia by extension to the veins from the intestines. No cardiac involvement was mentioned. Uhr[4] reported recovery of A. bovis, identified by cultural characteristics, from the blood stream and from vegetations on the mitral valve.

All in all, 4 cases have been reported in which symptoms of subacute endocarditis were considered to be due to higher forms of bacteria and in which there was no evidence as to the portal of entry. It is to be remembered that Uhr stated that his case was indistinguishable both clinically and pathologically from "an ordinary case of subacute bacterial endocarditis." Naeslund,[12] Emmons[20] (who also referred to the work of Lord and Wright) and others have shown the presence of Actinomyces in the flora of human mouths and tonsillar crypts. In reference to these findings, Carrión[17] stated that he thought it reasonable to expect a larger number of actinomycotic infections in human disease. It may possibly be that these sources serve as portals of entry.

In reference to inoculation of animals, Jervell, Uhr and Basu reported no success. Alestra and Girolami reported recovery of an organism in their case 2 from guinea pigs and rabbits which died twenty-four hours after inoculation. Gose[21] reported no success. Carrión reported no

17. Carrión, A. L.: Actinomycosis in Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med. **13**:367-382, 1938.

18. Freed, D. F., and Light, F.: Generalized Actinomycosis with Positive Blood Cultures, Pennsylvania M. J. **36**:25-29, 1932.

19. Brunn, E.: Et tilfælde av aktinomykose pyæmi, Hospitalstid. **81**:16-20, 1938.

20. Emmons, C. W.: The Isolation of Actinomyces Bovis from Tonsillar Granules, Pub. Health Rep. **53**:1967-1975, 1938.

21. Gose, C. A.: A Case of Constrictive Pericarditis Due to Actinomycosis, Memphis M. J. **16**:56-58, 1942.

specific lesions. In a survey of the rest of the available literature I failed to find any reports of "takes" in animals, as the diagnosis was based on finding the granules in histologic sections or in the exudates in the cases of actinomycosis of the heart by secondary involvement from a distant primary focus. The literature is also scant in reference, to cultural findings in these cases. · Tubbs and Turner [22] reported cultures of Streptothrix in typical A. bovis form from the sputum and from abscesses of the pericardial sac. Genthner and Pendleton [23] referred to Actinomyces cultured from the purulent pleural surface.

Direct smears or histologic sections prepared from cardiac and associated lesions which showed coccal or bacillary forms have been reported in a few cases. Paltauf,[24] as early as 1890, mentioned finding gram-positive coccal structures, small bent rods and branching filaments in the pus of the metastatic abscesses and in the branches of the pulmonary artery without finding the granules in these areas. Numerous granules, however, were present in the pus of the pericardial exudate. Paetzold [25] referred to Richter's case in which cocci in chains were observed. Jervell described gram-positive coccoid rods in the spleen and structures of the same type in the histologic section of the heart valve, where some of these structures occurred in · chains. Uhr described a bacterial clump in an ateriole.

Although it is known that Actinomyces is pleomorphic, the conclusion cannot be drawn from smears or histologic sections alone that the coccal, bacillary and unbranched filamentous forms belong to the developing stages of Actinomyces unless cultures substantiate this. In regard to the second case reported in this paper it is quite reasonable to assume that these various forms belonged to the same strain of Actinomyces, because of the branching filamentous structures present and the coccal and bacillary forms diffusely spread out among the inflammatory cells, which is consistent with the picture of cellular response to infection rather than with that of contamination. Again, the clinical course was not that of an acute infection with a pyogenic bacterial organism. The cultural findings tie in with the foregoing description, although the organism was not recovered in pure culture at the first isolation.

The credit of originally suspecting the organism to be of the genus Actinomyces goes to Dr. W. K. Bell, the intern who made a smear of the vegetations of the heart valve and noticed the filaments. Although

22. Tubbs, O. S., and Turner, J. W. A.: Primary Actinomycosis of the Thorax, St. Barth. Hosp. J. **44**:184-188, 1937.

23. Genthner, W. M., and Pendleton, R. K.: Pulmonary Actinomycosis: A Report of Two Cases, New York State J.·Med. **32**:1283-1287, 1932.

24. Paltauf, R.: Wien. klin. Wchnschr. **3**:487, 1890.

25. Paetzold, P.: Ein Fall von generalisierter Aktinomykose beim Menschen, Frankfurt. Ztschr. f. Path. **16**:415-440, 1914-1915.

definite and strict orders had been left with the department that all autopsied heart valves should be submitted to me, my attention was not called to the specimen until the following day. This is mentioned merely to indicate specifically how easily such an infection could be overlooked through inadequate observation or a slip in technical procedure. If this point is carried across, the laboratory mistake in this instance would be of considerable value. It is impossible to surmise how many cases may have been diagnosed as cases of subacute bacterial endocarditis by history and histologic sections alone in the absence of cultures, or in the presence of sterile cultures not kept sufficiently long or only aerobically, or in the presence of inadequately prepared cultures. Branching forms took sixteen days for recognition in the cultures of case 1, and chlamydospores were not observed before twenty-six days' growth of the culture of the heart valve. The presence of chlamydospores should not be alarming. They have been mentioned as occurring in strains of Actinomyces by Dodge,[9] and they have been observed in other strains by me.[6] It is not intended to convey the thought that cardiac actinomycosis will be found in great numbers of cases by improved technic and care, but it is certain that the results will at least be more reliable. To achieve this, it is just as important to scrutinize closely the structures of the organism in tissue sections with the oil immersion objective of the microscope.

From the animal experimentation in case 1 attention is called to the coccal and bacillary forms in tissues of the rat. No filaments were found in these tissues, whereas in cultures of the organism filaments and chlamydospores developed. The similarity of microscopic changes in tissues of animals inoculated with cultures of a strain of A. bovis is discussed in another paper.[6]

Pathologic involvement of lymph nodes associated with cardiac actinomycosis is mentioned by Ruhräh,[26] Kissling[27] (*Die obduktion ergab Mediastinitis und Lymphadenitis actinomycotica mit Durchbruch in die Vena cava super* [The autopsy disclosed actinomycotic mediastinitis and lymphadenitis with a break-through into the vena cava superior]), Werthemann.[28] Gose[21] and Cornell and Shookhoff.[1] The picture of the pathologic changes varied from one that was nonspecific to that described by Kissling. I[6] have recovered strains of Actinomyces[29] from cultures of specimens of spinal fluid and of pus of brain

26. Ruhräh, J.: Actinomycosis in Man, Ann. Surg. **30**:438-440, 1899.

27. Kissling: Biologische Abteilung des ärztlichen Vereins in Hamburg, München. med. Wchnschr. **56**:207-208, 1909.

28. Werthemann, H.: Ueber die Generalisation der Aktinomykose, Virchows Arch. f. path. Anat. **255**:734, 1925.

29. Harley, R. D., and Wedding, E. S.: Syndrome of Uveitis, Meningo-Encephalitis, Alopecia, Poliosis, and Dysacousia: Report of a Case Due to Actinomyces, to be published.

abscesses showing rods bearing a morphologic resemblance to those observed in the lymph node of the rat inoculated in case 1.

The clinical course in case 1 simulated that of rheumatic endocarditis for some time, but the type of fever curve was recognized as unusual. The rises of temperature responded for over fifteen months to sulfonamide drugs. The clinical picture was considered that of subacute endocarditis.

The clinical course in case 2 was that of typical hypertensive cardiovascular disease, with decompensation, terminal renal damage and azotemia. Any evidence of subacute endocarditis was not recognized by the attending physician. That this condition was present and active was illustrated by the histologic picture of the valve section from autopsy. However, the predominant findings from the first-mentioned condition, together with the physiologic effects produced by a ruptured aortic cusp, may have masked any symptoms of the subacute endocarditis present. How long the subacute endocarditis had been present is difficult to estimate. Certainly, it was not the cause of death in this case. Evidence of inactive rheumatic heart disease was present.

SUMMARY

A review of literature disclosed reports of 4 cases in which there was a clinical picture of subacute bacterial endocarditis due to the higher forms of bacteria without any evidence of a portal of entry.

Of the 2 cases of actinomycotic endocarditis reported in this paper, one was characterized by the clinical picture of subacute endocarditis. The other case was not recognized before autopsy. The patient died of hypertensive heart disease with renal failure and azotemia. Evidence consistent with inactive rheumatic heart disease was present.

In case 1, inoculation of a rat produced pathologic evidence of infection with Actinomyces, and the organism was recovered in pure culture from the inoculated animal. Coccal structures, rods, filaments and branching filaments were observed in vegetations of the aortic valve in case 2. An aerobic strain of Actinomyces was recovered from the valve, but contaminants were present in the original culture. Nevertheless, the smears, the histologic sections and the cultures, together with the clinical history of the case, have been considered as supplying adequate evidence for a diagnosis of actinomycotic endocarditis.

It is important in such cases that laboratory procedures and technic be carried through completely, exactly and carefully, to exclude sources of error that may lead to failure of recognizing actinomycotic infections. A review of the literature shows that there is ample room for improvement in this respect.

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CARDIAC MANIFESTATIONS OF TOXIC ACTION OF EMETINE HYDROCHLORIDE IN AMEBIC DYSENTERY

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THE TOXIC action of emetine hydrochloride on the cardiovascular and neuromuscular systems has been well known for many years. In 1916 Levy and Rowntree [1] demonstrated by means of the electrocardiograph that an overdose of emetine hydrochloride in rabbits caused death by ventricular fibrillation. More recently Boyd and Scherf [2] observed intraventricular block, inversion of T waves and cardiac arrhythmias in experimental intoxication with emetine hydrochloride in cats.

In human beings the toxic effects of emetine hydrochloride on the neuromuscular system have been described more frequently than the cardiac manifestations. These consist principally in generalized muscular weakness, tremors and peripheral neuritis. Diarrhea, which may be bloody in severe conditions, vomiting and abdominal cramping pains are among the other commoner evidences of toxicity of emetine hydrochloride.

Although it has been well established that the long-continued administration of emetine hydrochloride in large doses in human beings will generally result in the development of signs of toxicity, it has not been sufficiently emphasized that the usual therapeutic dose may also produce serious injury. The great majority of reported fatalities in human beings have resulted from the administration of 20 grains (1.29 Gm.) or more, but six deaths have been reported after a total of only 10 grains (0.65 Gm.).[3] Furthermore, it has been pointed out[4] that the margin of safety between the effective and the toxic dose of emetine

1. Levy, R. L., and Rowntree, L.: On the Toxicity of Various Commercial Preparations of Emetine Hydrochloride, Arch. Int. Med. **17**:420 (March) 1916.

2. Boyd, L. J., and Scherf, D.: The Electrocardiogram in Acute Emetine Intoxication, J. Pharmacol. & Exper. Therap. **71**:362, 1941.

3. Heilig, R., and Visveswar, S. K.: On the Cardiac Effects of Emetine, Indian M. Gaz. **78**:419, 1943; abstracted, Trop. Dis. Bull. **41**:285, 1944.

4. Sollmann, T. H.: A Manual of Pharmacology and Its Application to Therapeutics and Toxicology, Philadelphia, W. B. Saunders Company, 1942.

hydrochloride is small. This has been partially attributed to the cumulative action of emetine hydrochloride resulting from its slow excretion through the kidneys and the intestinal tract.

Recent reports of the clinical effects of administration of emetine hydrochloride in several large series of cases have tended to minimize the risks of toxic reactions. In 1935 Brown[5] reported that of 554 patients with amebic dysentery treated with emetine hydrochloride toxic reactions, principally peripheral neuritis, developed in only 23. There were reactions in only 3 of those treated with 10 grains (0.65 Gm.) or less. In addition, he found only thirty-seven reported instances of toxicity of emetine hydrochloride in the literature prior to 1935, with ten deaths. Similarly, Heilig and Visveswar[3] failed to observe any significant alteration in the electrocardiogram, blood pressure or orthodiagram of 14 patients treated with twelve intramuscular injections of 1 grain (0.06 Gm.) of emetine hydrochloride daily. In a series of 72 patients treated by Hardgrove and Smith[6] in the Panama Canal Zone, only one serious cardiac effect, resembling cardiac infarction, was observed after ten intramuscular injections of 1 grain daily. Electrocardiographic changes developed in 53 per cent of the patients, the vast majority affecting the T waves; actual inversion of the T waves occurred in only 13 per cent. Hardgrove and Smith concluded that emetine hydrochloride in therapeutic doses produces only minor and transient electrocardiographic changes and that there is little risk involved in the use of emetine hydrochloride if electrocardiograms are taken during the course of treatment and the patient is kept in bed.

We have recently had the opportunity to observe 9 patients in whom toxic cardiac effects developed after the administration of emetine hydrochloride for amebic dysentery. These are reported in detail in order to reemphasize the possible danger in the administration of emetine hydrochloride and the precautions necessary during treatment.

MATERIAL

In November and December 1944 there were 21 patients recently treated with emetine hydrochloride for amebiasis in other medical installations who came under our observation. Only 4 of these patients had had electrocardiograms during the course of emetine hydrochloride therapy. Electrocardiograms were obtained on all patients on their admission to the hospital, and 8 of the 21 patients were found to have a distinctly abnormal record. Two of the patients had electrocardiograms that were considered borderline, and in the remainder no abnormali-

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5. Brown, P. W.: Results and Dangers in the Treatment of Amebiasis: A Summary of Fifteen Years' Clinical Experience at the Mayo Clinic, J. A. M. A. **105**:1319 (Oct. 26) 1935.

6. Hardgrove, M., and Smith, E. R.: Effects of Emetine on the Electrocardiogram, Am. Heart J. **28**:752, 1944.

ties were found. Serial records at intervals of one to two weeks were obtained in the first two groups. An additional patient, admitted to our hospital at a later date, demonstrated toxic myocardial changes due to emetine hydrochloride and is included in this series. Three of the patients in the first group manifested obvious neuromuscular symptoms and signs, cramping abdominal pains and diarrhea that could be ascribed to toxicity of emetine hydrochloride. This report is based on a study of these 9 cases. The outstanding clinical features are listed in the table.

SUMMARY OF FINDINGS

Dose of Emetine.—The total dose of emetine hydrochloride administered prior to admission of the patients to the hospital ranged from 7 to 22 grains (0.45 to 1.42 Gm.). One patient (case 9) showed electrocardiographic changes after the administration of only 4 grains (0.26 Gm.) and received a total of 7 grains (0.45 Gm.). Two patients received a course of ten daily injections of 1 grain (0.06 Gm.) of emetine hydrochloride. Four patients received a total of 14 grains (0.91 Gm.), 2 in consecutive daily injections and 2 with a rest period of seven and ten days following the tenth injection. One patient had received 19 grains (1.25 Gm.) with a twelve day rest period following the fifth injection, and 1 patient had received a total of 22 grains (1.42 Gm.) administered in three courses over a period of thirty-four days.

Time of Appearance of Toxic Signs.—Whereas the neuromuscular manifestations of toxicity usually appeared during the period of administration of emetine hydrochloride, the time of the appearance of the abnormal electrocardiographic changes was difficult to ascertain. Control electrocardiograms were available in only 4 instances. In case 9, changes were noted after administration of only 4 grains (0.26 Gm.). In case 6, normal records were obtained after 6 and 12 grains (0.39 and 0.78 Gm.) were given, and an abnormal electrocardiogram was not demonstrated until three weeks after the discontinuance of the use of emetine hydrochloride. Similarly, normal electrocardiograms were obtained at the completion of courses of 14 and 19 grains (0.91 and 1.23 Gm.) of emetine hydrochloride in cases 1 and 4, but subsequent records were demonstrated to be abnormal. In the remaining 5 cases without control records, the first abnormal electrocardiogram was observed from two to seventeen days after the last injection of emetine hydrochloride.

Electrocardiographic Changes.—The commonest electrocardiographic abnormality observed was inversion of the T waves, usually involving all the standard leads. The T waves in leads II and III were inverted in all the cases. The T wave in lead I was isoelectric or inverted in 6 cases, and the T wave in lead IV was inverted in 3 cases. Deviation of the S-T segment was rare, consisting usually in minimal depression; eleva-

Summary of Findings in Nine Patients with Amebic Dysentery Presenting Toxic Effects Following Administration of Emetine Hydrochloride

Case	Age, Yr.	Emetine Hydrochloride Total Dose, Grains	Emetine Hydrochloride Dates Given	Toxic Manifestations Neuromuscular	Cardiac Signs	Electrocardiographic Changes	Time of First Abnormal Electrocardiogram	Duration of Electrocardiographic Change	Other Toxic Symptoms
1 (G. R. M.)	28	18	10/23 to 11/5 11/15 to 11/18	Generalized weakness, tremors, dysarthria, dizziness	Dyspnea on mild exertion, palpitation, tachycardia; gallop rhythm; apical systolic murmur	T_1 low; T_2 and T_3 inverted	11/30	5 wk.	Diarrhea and abdominal pain
2 (R. H. B.)	25	22	10/14 to 10/18 10/21 to 11/4 11/15 to 11/18	Generalized weakness, most decided in pelvic and shoulder girdles; tremor of hands	Dyspnea and tachycardia on exertion; soft apical systolic murmur	T_1 isoelectric; T_2, T_2 and T_4 inverted; QRS_4 W shaped	11/20	Over 2 mo.	Diarrhea and abdominal pain
3 (E. W.)	30	14	11/3 to 11/17	Moderate generalized weakness	Dyspnea on exertion	T_1 and T_4 semi-inverted; T_2 and T_3 deeply inverted and coveplane	12/3	Over 5 mo.	
4 (K. H. E.)	20	18	10/20 to 10/24 11/6 to 11/19	Weakness of the abductors and adductors, thighs and gluteal muscles	Dyspnea on exertion	T_1 isoelectric, T_2 and T_3 diphasic	12/3	2 mo.	
5 (L. S. J.)	30	10	11/14 to 11/24	None	Mild dyspnea on exertion	T_1 flat; T_4 inverted; QRS_2 and QRS_3 W shaped	12/10	Over 2 mo.	
6 (G. K.)	37	15	11/1 to 11/10 11/16 to 11/20	Generalized muscular aching and weakness; hyperreflexia, tremor of extremities	None	T_1 low; T_2 and T_3 diphasic	12/14	6 wk.	Diarrhea and abdominal pain
7 (J. M.)	30	10	11/18 to 11/27	None	None	T_1 flat; T_2 diphasic; T_3 inverted	12/10	Over 2 mo.	
8 (K. C.)	25	14	11/6 to 11/18	None	Tachycardia on exertion	Small Q_3; T_2 low; T_3 inverted	12/5	About 6 wk.	
9 (O. O. A.)	24	7	5/30 to 6/6	Generalized weakness, nervousness; tremor of hands	Palpitation, soft apical systolic murmur	T_1 low; T_2 and T_3 inverted	6/3	Over 1 mo.	

tion of the S-T segment was not observed. Abnormalities in the QRS complex occurred in 2 cases and consisted in deep Q waves in leads II and III in 1 case and a W-shaped QRS complex in lead IV in the second case. Prolongation of the P-R interval or significant cardiac arrhythmia was not observed.

The duration of the abnormal findings varied considerably but was usually prolonged. In 3 cases the electrocardiogram returned to normal from four to six weeks after the abnormalities were first noted, and in 2 the abnormalities disappeared after two months. The other patients evacuated from the hospital after periods varying from one to four months still had abnormal records at the time of transfer.
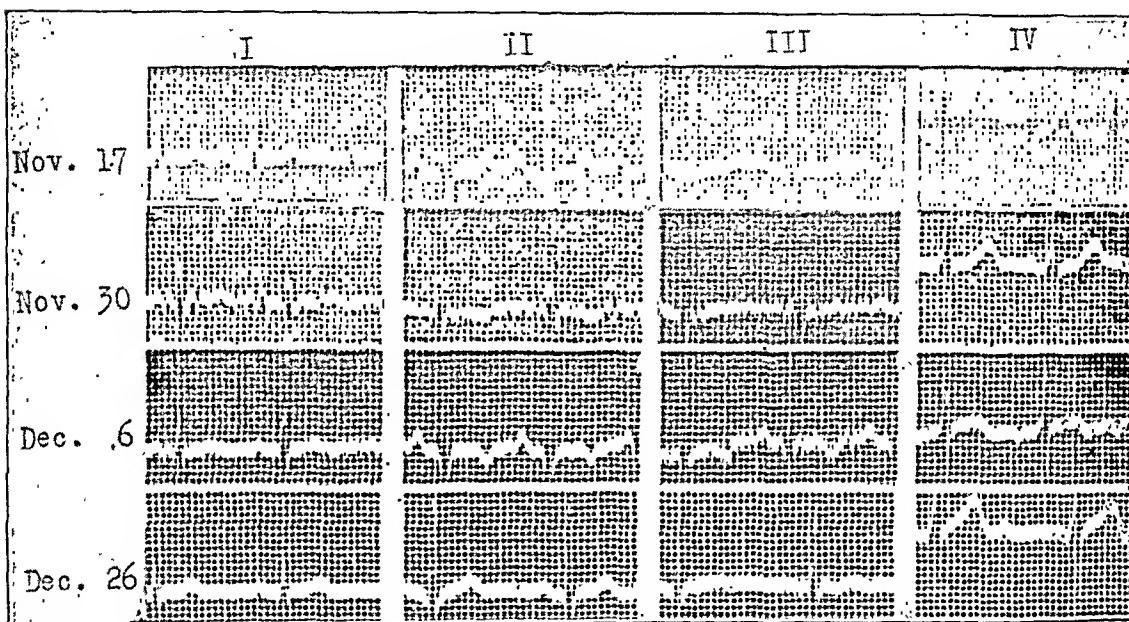
Fig. 1 (case 1).—The patient, Sgt. G. R. M., aged 28, had amebic dysentery treated with emetine hydrochloride, 18 grains (1.16 Gm.) intramuscularly, 1 grain daily from October 23 to November 5 and from November 15 to 18. The electrocardiogram shows lowering of the T waves in leads I and IV and deep inversion of the T waves in leads II and III. By December 26 the record had returned to normal. Note the artefacts on November 30 and December 6 produced by the patient's muscular tremor.

Cardiac Examination.—Generally the clinical examination of the cardiovascular system was not strikingly abnormal. Moderate tachycardia in patients at rest and after mild effort was observed in 3 cases, and in 1 (case 1) it was associated with presystolic gallop rhythm. Mild precordial discomfort occurred in 1 patient, and dyspnea and fatigue on exertion of various degrees were a presenting symptom in 5 instances. None of the patients showed any abnormality in the size or configuration of the heart by roentgenologic examination. No significant lowering of the blood pressure was noted in this series.

Neuromuscular Manifestations.—Generalized muscular weakness and tremor, involving particularly the lower extremities, developed in 5 patients. In 1 patient (case 1) the neuromuscular weakness was incapacitating and was manifested by decided coarse tremor of the extremities, lips and tongue, difficulty in speech, weakness of the upper and lower extremities and generalized hyperreflexia. The patient in case 2 exhibited similar abnormalities, but they were of lesser severity.
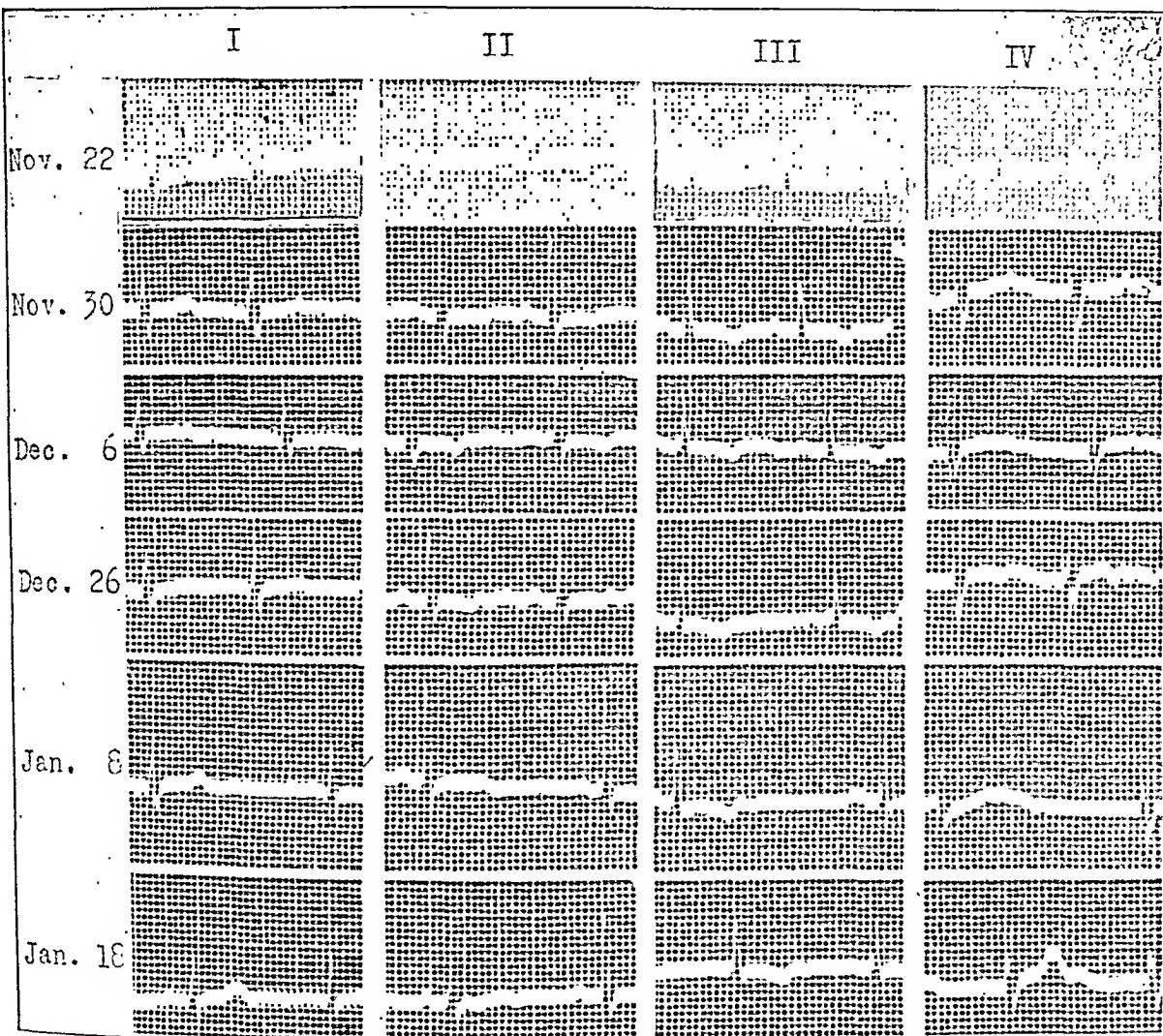
Fig. 2 (case 2).—The patient, Pvt. R. H. B., aged 25, had amebic dysentery treated with emetine hydrochloride, 22 grains intramuscularly, 1 grain daily from October 14 to 18, October 21 to November 4 and November 15 to 18. The electrocardiogram shows isoelectric T waves in lead I, inverted T waves in leads II, III and IV, a small R wave in lead IV and a polyphasic QRS complex. The record of January 18 is normal except for slight lowering of the T wave in lead II and inverted T wave in lead III.

Three other patients complained of generalized weakness, but there were less striking objective findings. Abnormal reflexes or sensory changes were not observed.

Gastrointestinal Symptoms.—In 3 instances, nonbloody diarrhea recurred during the course of treatment in association with neuromuscular symptoms of toxicity. There was cramping abdominal pain in each instance. No further antiamebic therapy was administered to the patients, and the symptoms disappeared spontaneously when the use of emetine hydrochloride was discontinued.
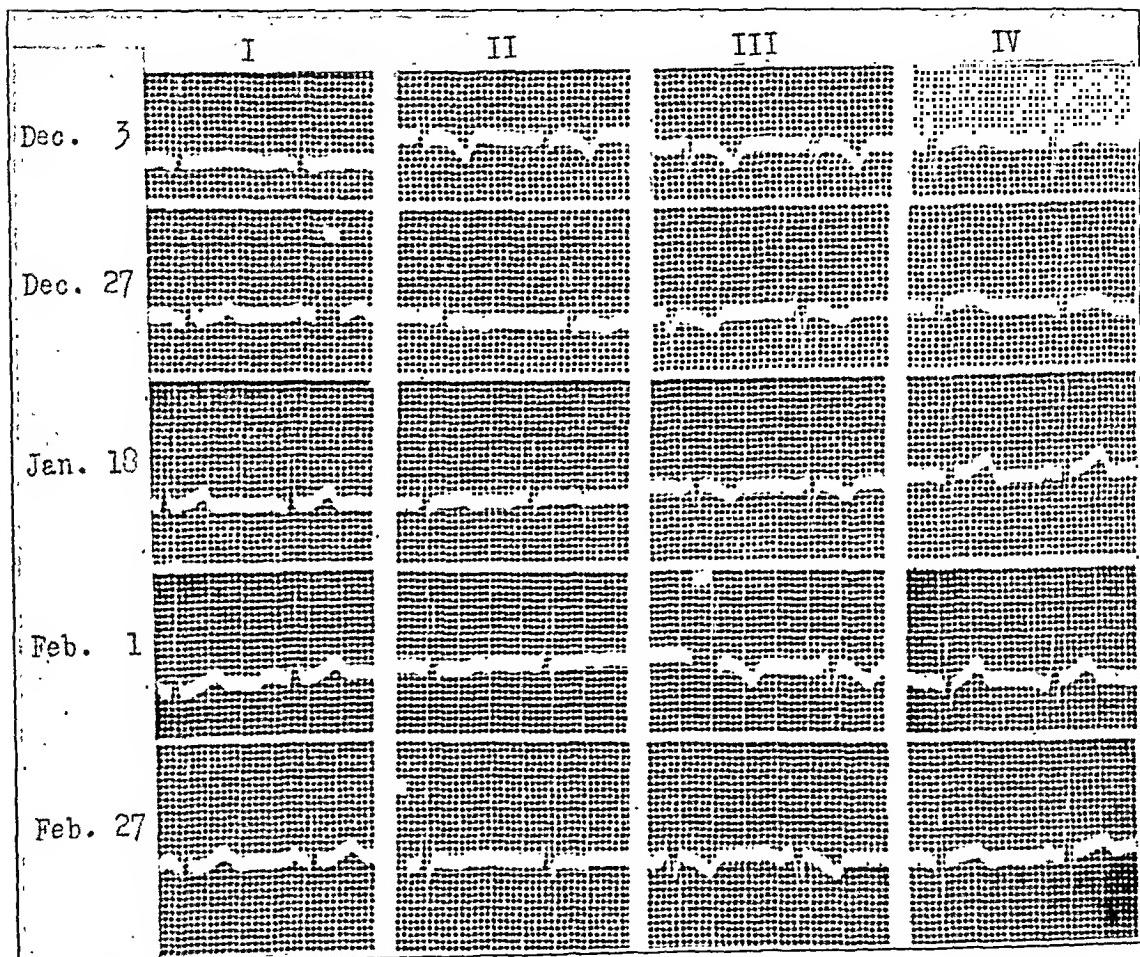
Fig. 3 (case 3).—The patient, Pvt. E. W., aged 30, had amebic dysentery treated with emetine hydrochloride, 14 grains intramuscularly, 1 grain daily from November 3 to 17. The electrocardiogram shows a low T wave in lead I, deeply inverted T waves in leads II and III and a diphasic T wave in lead IV. A semi-inverted. T wave in lead II and an inverted T wave in lead III are still present on February 27.

COMMENT

It is evident from the cases presented that electrocardiographic changes, clinical signs of cardiac damage and neuromuscular disturbances occur not infrequently after the administration of emetine hydrochloride. The electrocardiograms in our cases were generally obtained at the end of the course of treatment or from several days to two weeks

after the last injection. It is probable that had more frequent records been obtained during the course of treatment electrocardiographic changes would have been demonstrated oftener. We have recently treated 3 additional patients with emetine hydrochloride and have demonstrated electrocardiographic changes in the form of inversion of the T waves after administration of a total of 5 and 6 grains (0.32 and 0.39 Gm.). Use of the drug was promptly discontinued, and the abnormalities disappeared within one to two weeks.

Although electrocardiographic changes may occur after administration of as little as 3 or 4 grains (0.19 or 0.26 Gm.) of emetine hydrochloride, we were struck by the fact that at times they did not appear
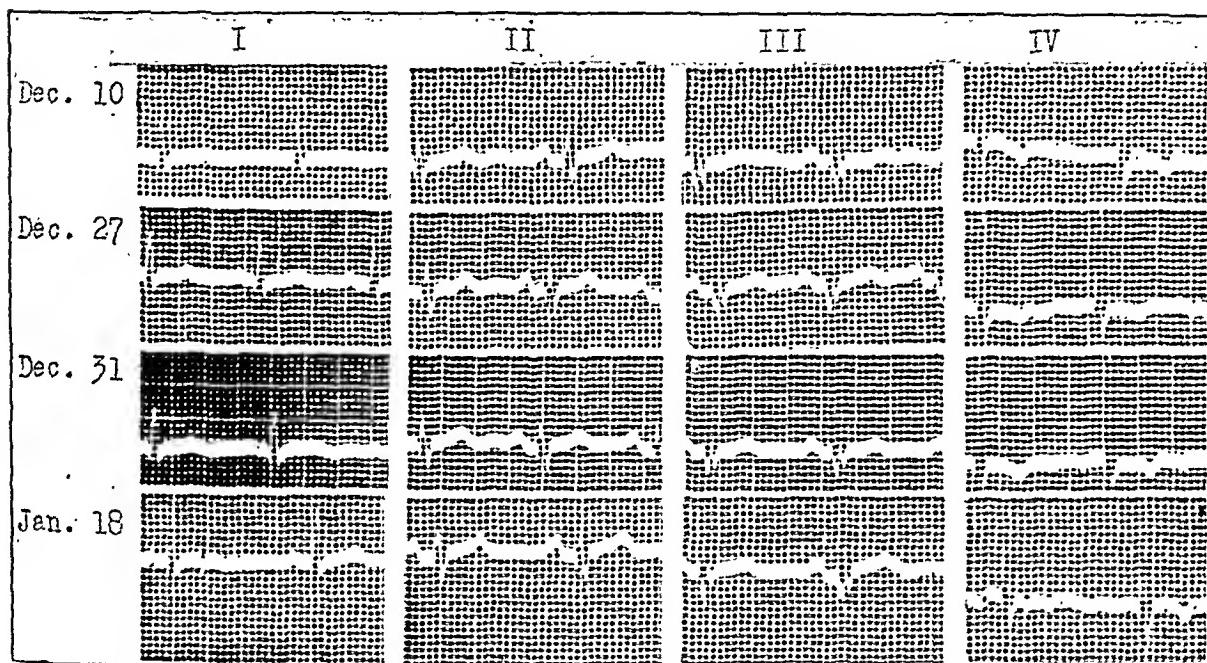
Fig. 4 (case 5).—The patient, Pfc. L. J., aged 30, had amebic dysentery treated with emetine hydrochloride, 10 grains intramuscularly, 1 grain daily from November 14 to 23. The electrocardiogram shows a low T wave in lead I, an inverted T wave in lead IV and a polyphasic W-shaped QRS complex in leads II and III. The abnormal T wave in lead IV and QRS complex are still present on January 18.

until the entire course had been completed. In 3 of the cases an electrocardiogram was normal after 12, 14 and 19 grains (0.78, 0.91 and 1.23 Gm.) of emetine hydrochloride respectively were administered, but a record obtained one to two weeks after the cessation of treatment presented distinct changes. Thus there may be a lag in the time of the appearance of the electrocardiographic abnormalities, and the absence of such changes cannot always be utilized as a criterion for the continued administration of emetine hydrochloride with impunity beyond a certain level of dosage. Were one to wait until electrocardiographic changes developed before discontinuing the drug, increased damage would result.

The appearance of tachycardia, fatigue or dyspnea on exertion, muscular weakness, tremor or any other toxic manifestation is an indication for the immediate discontinuance of emetine hydrochloride therapy, even in the presence of a normal electrocardiogram.

Another interesting observation in our cases was the relatively long duration of electrocardiographic abnormalities. In one half the cases the abnormalities persisted for two months or more after the cessation of treatment, and in no case was the duration less than one month. This suggests either that the emetine hydrochloride is fixed in the myocardium for a long period or that the toxic myocardial changes that it produces are on an anatomic basis. The underlying cause for the electrocardiographic changes and cardiac damage is probably myocardial degeneration. This has been demonstrated in experiments on animals in which depression of the cardiac muscle and actual myocardial necrosis have been observed, particularly after large doses or prolonged administration.[7] The electrocardiographic changes which we have described are nonspecific and resemble those seen in toxic, inflammatory or degenerative myocardial states due to other causes. In view of these findings, the interval of ten days to two weeks between courses, as sometimes advised, seems too brief, and it would be advisable to wait one to two months after a course of emetine hydrochloride has been completed before the course is repeated. If electrocardiographic changes are observed early in the course of treatment and use of the drug is discontinued immediately, there is reason to believe that the abnormalities disappear more rapidly and clinical toxic changes do not develop. This emphasizes the importance of frequent electrocardiograms during administration of emetine hydrochloride.

The dose required to produce toxic reactions varied in this series. This suggests that there is considerable variation in tolerance to the drug that can be ascribed to individual differences either in rate of excretion or in susceptibility. It has also been demonstrated in the past that different commercial preparations of emetine hydrochloride vary considerably in toxicity. This has been attributed by some to the presence in the preparation of a toxic product such as cephalin.[8] In the present series of cases it is known that a variety of commercial preparations were involved and that the incidence of toxic reactions cannot be ascribed to a single toxic preparation.

The cases presented in this report emphasize also the importance of differentiating between the diarrhea produced by the amebic dysentery

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7. Ghosh, B. N., and Adhya, P. C.: Some Newer Observations on the Pharmacology of Emetine, J. Indian M. A. **13**:37, 1943; abstracted, Trop. Dis. Bull. **41**:289, 1944. Scherf.[2] Levy and Rowntree.[1] Boyd and Sollmann.[4]

and that produced as a result of the administration of emetine hydrochloride. In several of the cases, the recurrence of diarrhea either during or shortly after the completion of a course of emetine hydrochloride was interpreted as being due to a recurrence of the disease and further anti-amebic treatment was deemed indicated. In each instance the diarrhea subsided spontaneously when treatment with the drug was discontinued. In most cases of true amebic dysentery improvement in the diarrhea is noted during the early phase of treatment; recurrence of diarrhea later in the course should lead one to suspect that this might be ascribed to the toxic effect of emetine hydrochloride.

The following regimen is recommended during the administration of emetine hydrochloride. It is our belief that the frequency of serious toxic manifestations would be decreased if it is followed. 1. The patient should be maintained on absolute rest in bed throughout the course of treatment. The importance of this is demonstrated by the patients in cases 1 and 2, who fainted or collapsed while walking in the area of the hospital. 2. The pulse rate should be recorded at frequent intervals daily and preferably graphed on the clinical record. Tachycardia may be the first clinical sign of toxic effect on the heart. 3. The patient should be examined and questioned at least daily for the detection of signs of toxicity such as diarrhea, fatigue, dyspnea on exertion, muscular tremors or weakness and dizziness. 4. It is advised that an electrocardiogram be taken before treatment is instituted and after the fifth grain. Another electrocardiogram should be obtained at the completion of the course of treatment and again one week later. Use of the drug should be promptly discontinued if significant changes are found. 5. It has been our clinical impression that in the majority of cases of amebic dysentery as great a therapeutic effect has resulted from the administration of 5 to 7 grains (0.32 to 0.45 Gm.) of emetine hydrochloride as has been obtained with higher doses sometimes recommended. 6. If clinical evidence of amebiasis persists after the first course of treatment and no evidence of toxicity of emetine hydrochloride has been observed, a rest period of at least a month should intervene prior to the resumption of treatment. If significant electrocardiographic changes or other clinical evidence of toxicity are observed during or after the first course of treatment with emetine hydrochloride, at least two months should be allowed to intervene before further emetine hydrochloride is administered. If that becomes necessary, electrocardiographic tracings should be made after the third grain is given. It would seem to be safer to resort to other forms of treatment for this group of patients. 7. Emetine hydrochloride should not be used in the presence of suspected organic heart disease and should be used with great caution in patients who are anemic and debilitated.

CONCLUSIONS

1. Nine cases of amebic dysentery are presented in which toxic cardiac manifestations developed after treatment with emetine hydrochloride in total doses varying from 7 to 22 grains (0.32 to 1.42 Gm.). These consisted .in fatigue, dyspnea and tachycardia on mild exertion and electrocardiographic abnormalities generally involving the T waves in all leads.

2. The dose of emetine hydrochloride required to produce toxic cardiac effects varied in each case, suggesting individual differences in susceptibility or in rate of excretion of the drug.

3. The time of appearance of the electrocardiographic abnormalities also varied in each case and was often delayed until one or two weeks following the discontinuation of treatment. Owing to this lag in the appearance of electrocardiographic changes, their absence cannot be safely utilized as a criterion for the continuation of emetine hydrochloride therapy beyond a certain dose.

4. The electrocardiographic abnormalities, when present, were of long duration, often persisting for two months or more following cessation of treatment, suggesting prolonged fixation of the drug in the myocardium or actual myocardial degeneration as the basis for the cardiac manifestations.

5. Toxic effects on the neuromuscular and gastrointestinal systems generally preceded the appearance of toxic cardiac effects. The former as well as the latter are indications for the discontinuance of further therapy with emetine hydrochloride.

6. A regimen is outlined for the management of amebic dysentery when emetine hydrochloride is employed, which, it is believed, will reduce the danger of toxic cardiac effects.

PENICILLIN IN THE TREATMENT OF KERATOSIS BLEN-NORRHAGICA · WITH POLYARTHRITIS

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THE PURPOSE of this communication is to present our observations on 3 cases of keratosis blennorrhagica treated with penicillin. To our knowledge, no record of this type of therapy for keratosis blennorrhagica has appeared so far in the literature. It is a rare condition, occurring approximately in the ratio of 1 in every 5,000 to 7,500 cases of gonorrhea.[1] To date, somewhat over 100 cases have been reported.

Many excellent reviews [2] of this disease have been published, and we shall not go into a detailed description of the lesions. The clinical syndrome is characterized by the triad of urethritis, arthritis and dermatosis.[3] The onset is insidious and follows chronic and recurrent attacks of gonorrheal urethritis. Chills and fever are present. The dermatitis is usually preceded by or associated with arthritis involving one or several joints. The lesions of the skin consist of vesicles, pustules and crusting associated with keratosis. The nails are commonly affected by pustules which develop under the distal portions. The pustules dry, forming hyperkeratotic crusts, which become heaped up and separate the nails from their beds.

REPORT OF CASES

CASE 1.—R. B., à 27 year old unmarried Negro man, was admitted to Bellevue Hospital on Oct. 5, 1944, complaining of "sores" on his fingers, hands, toes, feet,

1. Combes, F. C.; Dietrich, C., and Cohen, J.: Keratosis Blennorrhagica: A Brief Review and Report on the Effects of Hyperpyrexia in Its Treatment, J. A. M. A. 114:2078-2082 (May 25) 1940.

2. Herold, W. C., and Smith, D. C.: Keratosis Blennorrhagica: Report of Two Cases, Arch. Dermat. & Syph. 44:398-408 (Sept.) 1941. Epstein, E.: Differential Diagnosis of Keratosis Blennorhagica and Psoriasis Arythropathica, ibid. 40:547-559 (Oct.) 1939. Combes and others.[1]

3. Downing, J. C.: Keratoderma Blennorrhagicum: Report of a Case, J. A. M. A. 102:829-831 (March 17) 1934.

legs and scalp for three weeks, during which time all the nails had fallen off his fingers and toes. Simultaneously, his right knee had become swollen and painful.

In 1938, three days after sexual exposure, he noticed a urethral discharge. Several days later pain and swelling of the left wrist and hand appeared. At another hospital, gonorrheal urethritis and gonorrheal arthritis were diagnosed and treated with sulfonamide compounds. The discharge disappeared promptly, and
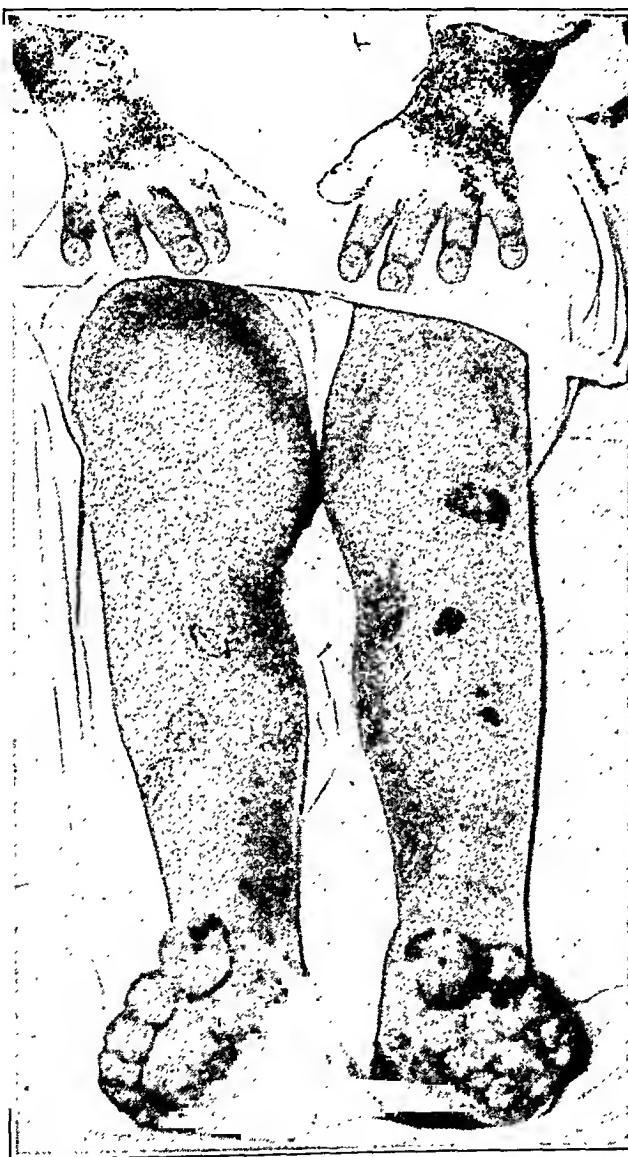
Fig. 1 (case 1).—Keratosis blennorrhagica showing typical lesions of the skin of hands and feet.

the arthritis improved. Since that time the patient has required hospital care on six different occasions for recurrence of pains and swelling of the joints, accompanied each time with a urethral discharge. In 1942 he was treated for conditions of the skin similar to those for which he was admitted to this hospital. After eleven months of hospitalization and varied treatment, the skin slowly cleared until there was no residuum.

He denied any sexual exposure since 1938. He stated that various joints had been involved during all the stages of his illness, including both knees, the left foot and both elbows and wrists.

The systemic review revealed no abnormalties, and the past history, other than that mentioned, was not pertinent. The family history was noncontributory.

Physical examination revealed a well nourished and well developed young Negro man with typical lesions of the skin of both hands and feet, involving all the fingers and toes (fig. 1). Lesions were present also on both legs, on the abdomen and on the scalp. All the nails of his fingers and toes had fallen off. The dermatitis consisted of discrete, hyperkeratotic papules and vesicles varying from 0.5 to 5 cm. in diameter. Some showed secondary infection with formation of pus.

The right knee was moderately swollen, warm and sore on pressure and on motion. Rectal examination revealed the prostate to be soft, boggy and tender, particularly over the median lobe. The remainder of the physical examination revealed normality.

The white blood cell count was 14,000 per cubic millimeter on his admission to the hospital and became normal with treatment. Examination of the urine showed no abnormalities. The Wassermann and Frei tests elicited negative reactions. The erythrocyte sedimentation rate was 19.0 mm. in one hour (Westergren). Prostatic massage yielded no fluid. Complement fixation tests for Gonococcus in the blood and in fluid obtained from the right knee elicited strongly positive reactions. Culture of the fluid from the right knee was sterile. Chemical examination of the blood showed 10.0 mg. of calcium, 2.03 mg. of phosphorus and 2.5 mg. of uric acid per hundred cubic centimeters. The acid phosphatase content was 3.8 units, and the alkaline phosphatase content was 3.1 units per hundred cubic centimeters. Culture of the pus from one of the lesions on the skin yielded Staphylococcus aureus. Consultation with the department of dermatology confirmed the diagnosis of keratosis blennorrhagica.

The temperature on admission was 100.6 F. and remained at this level until the ninth day in hospital, when penicillin therapy was instituted. The penicillin was administered intramuscularly, 10,000 units every three hours, day and night, for a total dose of 1,500,000 units. Before administration of penicillin was started, compresses of potassium permanganate were used. They partially cleared up the secondary infection of the skin.

The response to penicillin was good. Shortly after treatment was begun, the temperature fell to normal and remained so until the patient's discharge from the hospital. All pustular involvement of the skin disappeared promptly. The keratotic lesions resolved slowly, and no new ones formed. The hyperkeratotic crusts fell off and were slowly replaced by normal skin. Up to the time of discharge the nails had not yet grown back. A few minimal keratotic residua were still present on the extremities. The effusion of the knee joint, removed by tapping before penicillin therapy, did not return. Pain and tenderness of the joint were abolished and did not recur. The patient was discharged from the hospital on the twenty-fourth day. All efforts to contact him a year later for follow-up were unsuccessful.

CASE 2.—P. K., a 36 year old white man, was admitted to Meadowbrook Hospital on Aug. 23, 1944, with pain in the left knee and both wrists and an eruption on the wrists, which became slightly swollen. The fingers were stiff, and he was unable to move them. These complaints were followed by stiffness and pain in the left knee. At about the same time as the joints became involved

the rash appeared. He gave a history of two episodes of gonorrheal urethritis, the first at the age of 29 and the other at 30. The remainder of the history was irrelevant.

Physical examination revealed a well developed, well nourished white man who appeared chronically ill. The blood pressure was 160 systolic and 100 diastolic. The heart was not enlarged. The sounds were of good quality, and there were no murmurs. The remainder of the physical examination showed nothing abnormal excepting the extremities. There was severe pain on movement of the fingers, wrists and the left knee. The wrists were slightly swollen. Both legs were covered with many pustular lesions, which were also present on the buttocks.
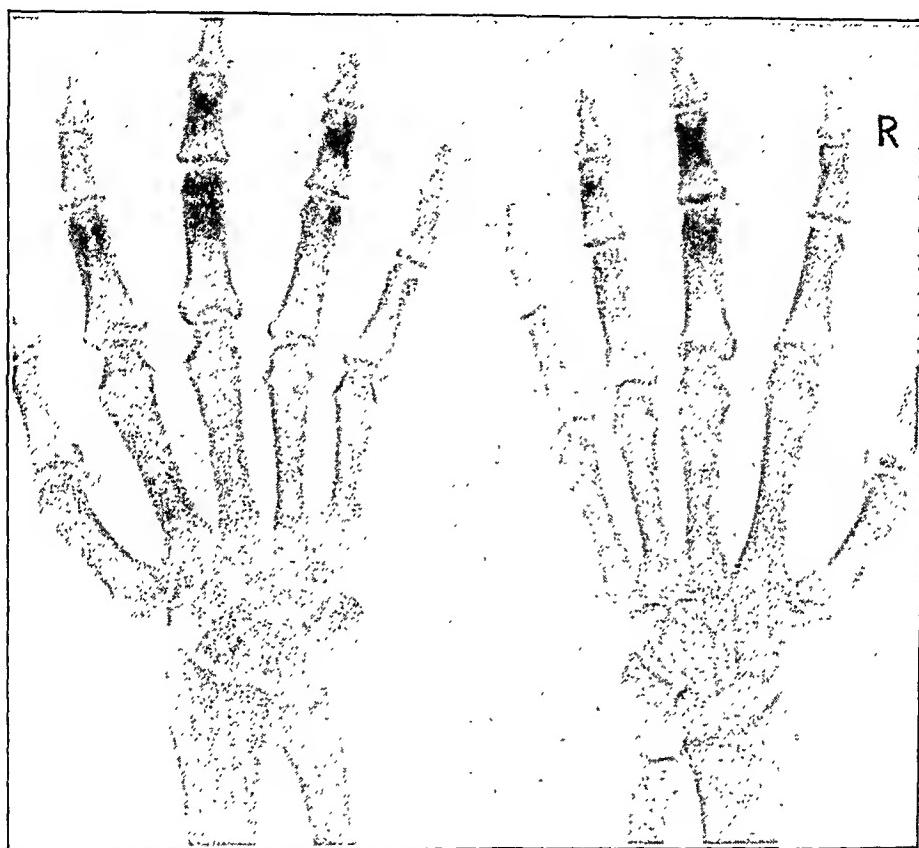
Fig. 2 (case 2).—Diffuse osteoporosis in the region of the carpal and metacarpal bones of the left hand and wrist, with narrowing of the spaces between the joints.

The blood cell count on admission showed a hemoglobin content of 82.2 per cent and a white blood cell count of 14,400, with 76 per cent polymorphonuclears, 22 per cent lymphocytes and 2 per cent monocytes. The white cell count was repeated on five occasions and varied between 8,100 and 18,200. The platelets numbered 310,000 per cubic millimeter. The nonprotein nitrogen content was 17 mg., the creatinine content 1.5 mg. and the sugar level 85 mg. per hundred cubic centimeters. The alkaline phosphatase content was 9.0 units and the acid phosphatase content 2.5 units per hundred cubic centimeters. The serum albumin-globulin ratio showed an inversion, with the albumin 3.7 Gm. and the globulin 5.1 Gm. per

hundred cubic centimeters. The result of the cephalin flocculation test was reported as positive (1 plus). The Wassermann and Kahn tests on the blood serum elicited negative reactions, and two cultures of the blood showed no growth. The sedimentation rate at intervals varied between 30 and 35 mm. in one hour (Cutler). Cultures taken from the lesions of the skin revealed no growth, and examination of prostatic smears gave normal results. Roentgenograms of the knee·joints did not reveal any abnormality of the bones or joints; the hands showed diffuse
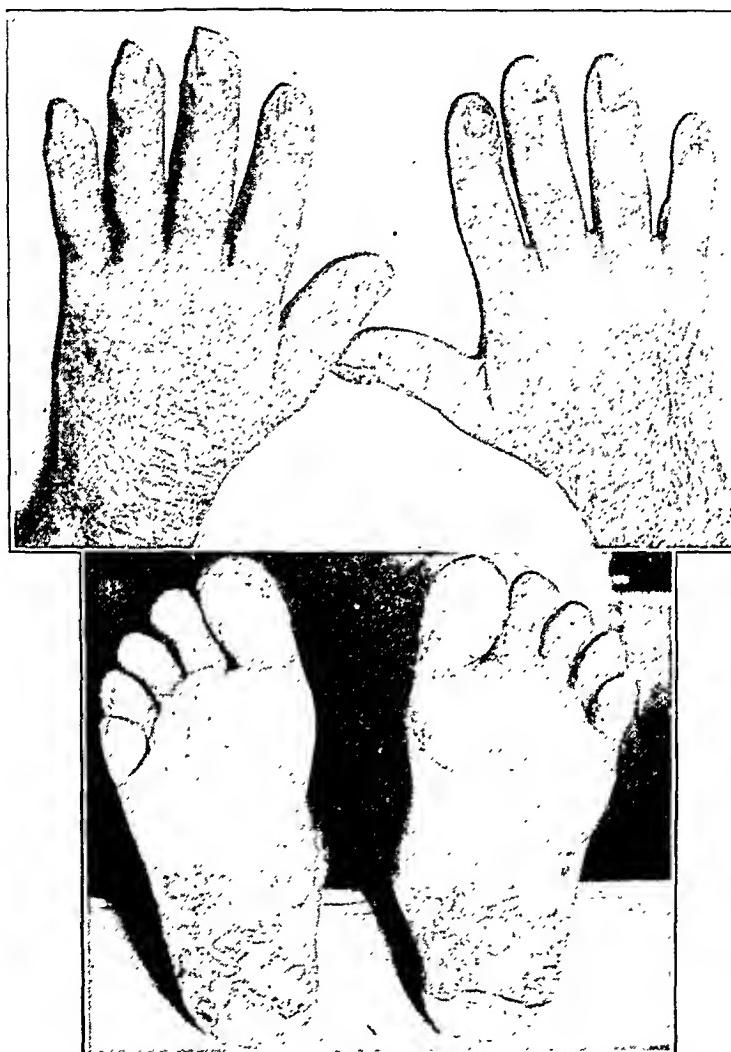
Fig. 3 (case 2).—Keratosis blennorhagica showing typical lesions of the skin of hands and feet.

osteoporosis in the region of the carpal bones and the adjacent portions of the metacarpals of the left hand and wrist, with narrowing of the spaces between the joints (fig. 2).

The temperature on his admission to the hospital was 100.8 F. and ranged between 99.5 and 102.5 F. The lesions of the skin spread to his hands and feet and involved the nails (fig. 3). The pains in the joints persisted, and movement provoked great discomfort. He was given large doses of salicylates, without relief of the pains in the joints.

On Sept. 28, 1944 administration of sulfadiazine was started, and a total of 20 Gm. was administered, without any response, the temperature remaining between 99.5 and 101.5 F.

On October 2 penicillin therapy was instituted.. He received 10,000 units intramuscularly every three hours for a total of 100,000 units. On October 5 the dose was increased to 20,000 units every four hours for seven doses. The total
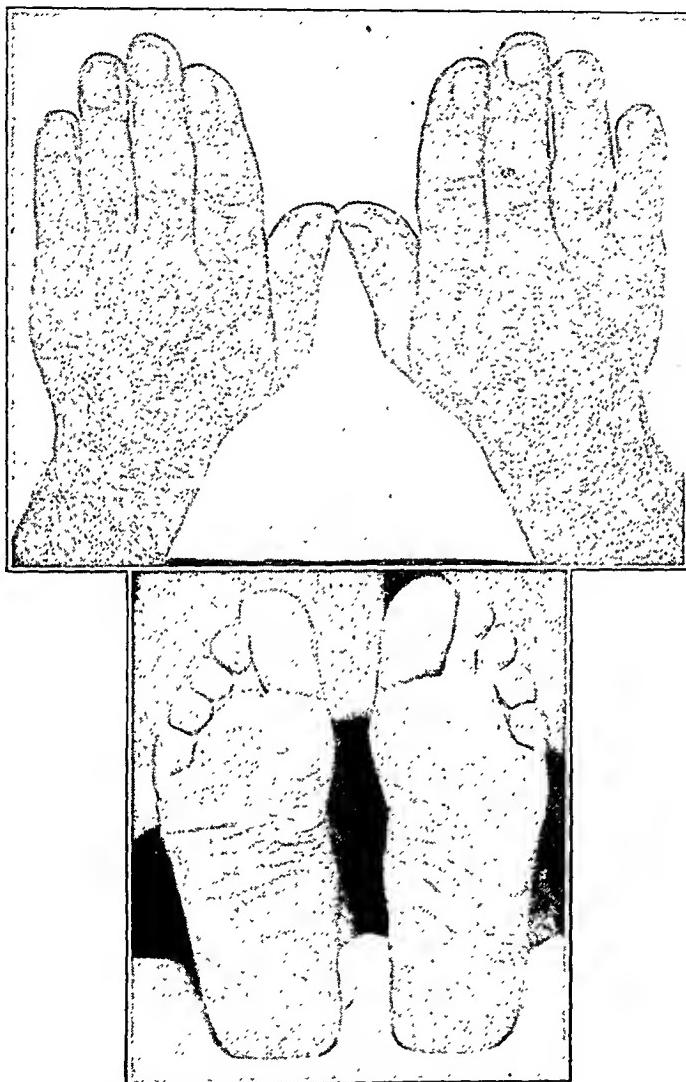
Fig. 4 (case 2).—Appearance of hands and feet one year after penicillin therapy.

amount of penicillin used was 240,000 units. On October 12 it was noted that the arthralgia and swelling of the joints had disappeared. The legs had improved, and his general condition was much better. The temperature had dropped to normal and remained there until the date of discharge.

The patient was seen again on Oct. 7, 1945, one year after his discharge from the hospital, for a follow-up examination. He stated that he continued to feel well after leaving the hospital. All the nails of his fingers and toes had fallen

off and had gradually been replaced by normal nails and tissues. Only a few pigmented areas could be seen on the feet (fig. 4). His only complaint was stiffness of the last three fingers of the left hand and soreness and swelling of the manubriosternal area. This joint was tender on palpation and felt enlarged. He was working as a truck driver and had not missed any time from work.

Roentgenograms of the hands and of the sternum at this time revealed a recalcification of the bones of the carpus, together with a discreteness of the carpal joints and carpal-metacarpal articulation, almost normal in appearance.

The manubriosternal articulation showed proliferative changes, with thickening of the periosteum for 2 inches (5 cm.) along the posterior surface of the articu-

Fig. 5 (case 2).—Recalcification of the bones of the carpus and a discreteness of the carpal joints and carpal-metacarpal articulation.

lating bones. Numerous erosions of the articulating margins were noticeable (figs. 5 and 6).

CASE 3.—A. G., a 32 year old white man, was admitted to Bellevue Hospital on June 6, 1944, complaining of pain "in all the joints" and a generalized cutaneous eruption lasting for about a year. On four previous occasions he had been admitted for the same complaints. The first attack of articular pain and swelling occurred in 1930, starting in the feet and spreading to almost all the joints of the body. Several weeks after the onset of polyarthritis a generalized cutaneous eruption developed. At this time a urethral discharge occurred, but gonococci were not demonstrated. The attack lasted fourteen months and was associated with chills and fever. He was symptom free after that period and had no residual manifestations of the joints or skin. In 1933 he suffered a similar attack of poly-

arthritis, without cutaneous manifestations. In 1935 there was a recurrence, similar to the first attack, with pains in the joints, fever and eruption of the skin. He was asymptomatic until April 1943, when he had his severest attack. At this time he had fever and polyarthritis for six weeks and a generalized cutaneous eruption for one week. He was acutely ill and suffered severe pains in the joints. He was treated for several weeks with vitamin A but showed only slight improvement. He then received a prolonged course of sulfonamide drugs, with little response. He signed out of the hospital, against advice, after one month. At this admission, one year later, he had grown progressively worse and was unable

Fig. 6 (case 2).—The manubriosternal articulation shows proliferative changes, with thickening of the periosteum.

to move. During that time he had experienced repeated shaking chills and fever. Almost all the peripheral joints showed contractures or deformity, and the generalized cutaneous eruption had grown worse. He was a complete invalid.

Physical examination revealed an acutely ill, emaciated and cachectic white man. There were flexion deformities of the hands, arms and legs. The wrists, elbows and knees were swollen, hot and tender. He was unable to move any of these joints. Over the arms, legs and pelvic regions there was an eruption of the skin, composed of dry, scaly, erythematous papules and circular patches. The finger nails and toe nails showed destructive changes (fig. 7). The remainder

of the physical examination disclosed no unusual condition. There was no urethral discharge.

The temperature varied between 100 and 103 F. The leukocyte count ranged from 10,200 to 20,000. The red blood cell count revealed moderate anemia. Analysis of the urine showed no abnormalities. Urethral culture failed to demon-
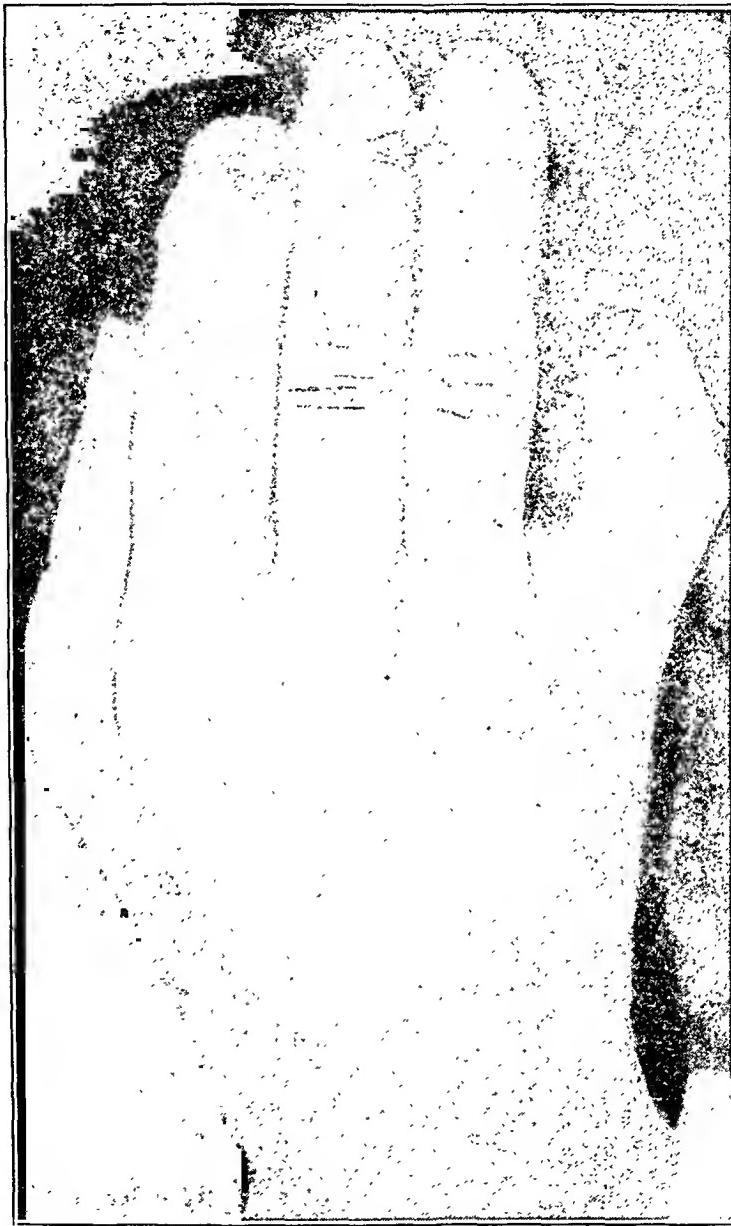
Fig. 7 (case 3).—Keratosis blennorrhagica showing typical lesions of the skin.

strate gonococci. The Wassermann reaction was negative, and the blood uric acid content was normal. Fluid obtained by tapping the knee contained 160,000 neutrophils per cubic millimeter, but culture of this material was sterile.

The patient was given rest in bed and treated symptomatically. During his stay in the hospital he remained bedridden and unable to move without pain. He again signed out, against advice, before penicillin therapy could be instituted.

On his final admission, on July 21, 1945, the patient was hospitalized in the Dermatology Service.[4]   His complaints were severe pains in the joints and a generalized cutaneous eruption which had continued since his previous admission. He had been bedridden since he left the hospital and had lost a considerable amount of weight. His appetite was poor, and he suffered intermittent diarrhea.

On physical examination he was emaciated and chronically ill. He lay motionless in bed, with his knees drawn up, unable to move without severe pain in all his joints. The skin of the extremities and the trunk was covered with crusting and scaling lesions. The fingers were stiff, and there was ankylosis of the knees and wrists, with atrophy of the periarticular soft tissues. The white blood cell count was 28,000 per cubic millimeter, with 80 per cent polymorphonuclears and 20 per cent lymphocytes. The red blood cells numbered 3,100,000 per cubic millimeter, and the hemoglobin content was 60 per cent. The temperature ranged from 100 to 102 F. for thirteen days and rose terminally to 106 F.

The patient was given general supportive therapy. He required considerable sedation with codeine and Demerol (1-methyl-4 phenyl piperidine 4-carbonic acid) because of the pain in the joints. He received activated viosterol, ferrous sulfate and dried yeast. On the third day in the hospital penicillin therapy was started. He received 40,000 units every three hours for a total of 1,440,000 units. Despite the treatment he became progressively worse. He became incontinent and refused to eat. Several infusions of dextrose, amigen and plasma were given, without any noticeable effect. He became confused, disoriented and incoherent and died on the fourteenth day in the hospital. The lesions of the skin and arthritis remained unchanged.

Permission for postmortem examination was refused.

COMMENT

The cases described meet the three criteria for a diagnosis of keratosis blennorrhagica: gonorrhea, arthritis and the characteristic cutaneous lesions.[1] Active urethritis is not essential. A history of previous gonorrheal infection (single or repeated) or evidence of definite pathologic changes in the genitourinary tract which are probably gonorrheal is said to fulfil the diagnostic requirement.[3]

Many forms of treatment have been advocated in the past, based on limited experience by various investigators. Local treatment is of little value. Surgical measures, such as drainage of foci in the prostate and seminal vesiculectomy, have been used. Autogenous vaccines were stated to be helpful.[5] Chemotherapy, in the form of administration of sulfanilamide and sulfarsphenamine, has been used, with indeterminate and inconsistent results.[1] Fever therapy by various means has been advocated.[6] Recently, large doses of vitamin A have been found effective.[7]

4. Dr. Frank C. Combes permitted us to include the final chapter in the history of this patient.

5. Scholtz, M.: A Syndrome of Blennorrhagic Keratoderma: Report of a Case, Arch. Dermat. & Syph. **15**:165-170 (Feb.) 1927.

Some of these patients present a chronic progressive cutaneous and articular disease, which in the past has continued relentlessly in spite of all previous methods of treatment, as in case 3. Often the disease is subject to natural remissions and recurrences, which make it difficult to evaluate conclusively any therapy not based on its employment in a large group of patients followed for a long time.

The effectiveness of any treatment in this disease must be gaged by its influence on the important manifestations: (1) the urethritis, (2) the arthritis, (3) the cutaneous eruption or keratosis and (4) the usual secondary infection of the lesions of the skin. Urethritis or a genitourinary focus was not demonstrable in our cases, but truly specific therapy would be expected to eradicate it when present. The arthritis resolved spontaneously in case 1 before penicillin therapy was begun. In case 2, the arthralgia and arthritis, although unrelieved by administration of salicylates, responded rapidly during penicillin therapy.

The cutaneous eruption and probably the secondary infection are apt to prove most resistant to treatment in the average case. The dermal suppuration was abolished with striking rapidity in cases 1 and 2. The keratotic lesions showed a therapeutic response which, even though not complete, surpassed the results from other measures reported.

The patient in case 2 required a much smaller amount of penicillin than the patient in case 1 for a favorable response. No definite statement, therefore, can be made as to the total dose to be given as a rule. Apparently it will have to be regulated individually according to the severity and responsiveness of the disease.

Final conclusions as to the value of use of penicillin in keratosis blennorrhagica cannot be drawn from these cases. The rarity of this condition makes it impossible for one group of investigators to assess properly any form of treatment. The early, thorough use of sulfonamide drugs and penicillin in the treatment of gonorrhea may reduce the incidence of this disease even further. The tendency to spontaneous remissions and recurrences in many of the cases emphasizes the need for cautious evaluation of any method of treatment unless employed in an adequate number of cases. The accumulation of further experience

6. (a) Epstein, E.: Hyperpyrexia in the Treatment of Keratoderma Blennorrhagicum, Am. J. Syph., Gonor. & Ven. Dis. **21**:148-154 (March) 1937. (b) Epstein, E., and Chambers, S. O.: Keratosis Blennorrhagica with Corneal Lesions: Further Observations on the Therapeutic Effect of Hyperpyrexia, Arch. Dermat. & Syph. **36**:1044-1051 (Nov.) 1937. (c) Combes and others.[1]

7. Combes, F., and Behrman, H.: Use of Vitamin A in Keratosis Blennorrhagica: Successful Treatment with Massive Doses; Report of a Case, Arch. Dermat. & Syph. **46**:728-733 (Nov.) 1942.

revealed in the literature should lead to reliable evaluation of the use of penicillin in the treatment of keratosis blennorrhagica.

Some similarities exist between this disease and so-called Reiter's syndrome. In 1916 Reiter [8] described a clinical picture characterized by the triad: urethritis, arthritis and conjunctivitis. He demonstrated a spirochete in the blood of his patient and called it "Spirochaeta forans." Since then, no spirochete or any other specific organisms have been found in any of the cases. According to the present consensus, the urethritis is felt to be nonspecific in character and is not venereal in cause. The arthritis may involve only one joint, but in most cases it is polyarticular.

Lesions of the skin similar to those seen in keratosis blennorrhagica have been observed in Reiter's syndrome.[9] Lever and Crawford [10] have reported a case of keratosis blennorrhagica without gonorrhea which they, felt might be a case of Reiter's disease. Conversely, cases of keratosis blennorrhagica have been reported [11] in which involvement of the eyes was present in addition to urethritis, arthritis and dermatitis.

The exact relationship between these two rather ill defined syndromes is not clear and remains open for further study. It is conceivable and worthy of consideration in any new investigation of this subject that Reiter's syndrome may be a variation of the classic clinical picture of keratosis blennorrhagica. The chief distinction at the present time is the widespread acceptance of the latter condition as gonorrheal in origin, while Reiter's syndrome is regarded as nonvenereal. The difference may well be resolved by future proof that gonorrheal infection in keratosis blennorragica occurs as a coincidental factor or acts as a predisposing agent in the causative process, actually producing pictures of both diseases and their variants.

CONCLUSIONS

Three cases of keratosis blennorrhagica are described. In 2 of the patients, treatment with penicillin gave a rapid and satisfactory response. The third patient did not submit to penicillin therapy until he was in a terminal state. Although our experience with the treatment has been impressive, the need for more extensive therapeutic study before final conclusions are drawn is emphasized.

8. Reiter, H.: Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica), Deutsche med. Wchnschr. **42**:1535, 1916.

9. Hollander, J. L.; Fogarty, C. W., Jr.; Abrams, N. R., and Kydd, D. M.: Arthritis Resembling Reiter's Syndrome: Observations on Twenty-Five Cases, J. A. M. A. **129**:593-595 (Oct. 27) 1945.

10. Lever, W. F., and Crawford, G. M.: Keratosis Blennorrhagica Without Gonorrhea (Reiter's Disease?), Arch. Dermat. & Syph. **49**:389-397 (June) 1944.

11. Chambers, S. O., and Koetter, G. F.: Keratosis Blennorrhagica, Arch. Dermat. & Syph. **27**:411-420 (March) 1933. Combes and others.[1]

News and Comment

THE ELLA SACHS PLOTZ FOUNDATION FOR THE ADVANCEMENT OF SCIENTIFIC INVESTIGATION

During the last year forty applications for grants were received by the Trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, of which twenty-nine came from the United States and the other eleven from seven different countries in Europe, Asia and North and South America.

In the twenty-three years of its existence the Foundation has made five hundred and fifty-one grants, which have been distributed to scientists throughout the world.

In their first statement regarding the purposes for which the Fund would be used, the Trustees expressed themselves as follows:

1. For the present, researches will be favored that are directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery.

2. As a rule, preference will be given to researches on a single problem or on closely allied problems; it is hoped that investigators in this and in other countries may be found whose work on similar or related problems may be assisted so that more rapid progress may be made possible.

3. Grants· may be used for the purchase of apparatus and supplies that are needed for special investigations and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which are ordinarily a part of laboratory equipment. Stipends for the support of investigators will be granted only under exceptional circumstances.

In the past few years the policy outlined in paragraph 2 of the Trustees' statement has been neglected, and grants will be given in the sciences closely related to medicine without reference to special fields. The maximum size of grants will usually be less than $500.

Applications for grants to be held during the year 1947-1948 must be in the hands of the Executive Committee before April 15, 1947. There are no formal application blanks, but letters asking for aid must state definitely the qualifications of the investigator, give an accurate description of the research and state the size of the grant requested and the specific use of the money to be expended. In their requests for aid applicants should state whether or not they have approached other foundations for financial assistance and what other sources of support are relied on for research. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done. Only applicants complying with these conditions will be considered.

Applications should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Fruit Street, Boston 14, Massachusetts, U. S. A.

THE FOURTH INTERNATIONAL CANCER RESEARCH CONGRESS

The Fourth International Cancer Research Congress will be held in St. Louis, Sept. 2 to 7, 1947. The Union International Contre le Cancer having accepted the invitation of the American Association for Cancer Research, the Congress will be held under the joint auspices of these two organizations, with Dr. E. V. Cowdry, Professor of Anatomy of the Washington University School of Medicine and Director of Research of the Barnard Free Skin and Cancer Hospital, serving as President of the Congress.

Of the previous congresses, the first was held in Madrid, Spain, in 1933; the second in Brussels, Belgium, in 1936, and the third in Atlantic City, N. J., in 1939. Because of the recent war there has not been a congress during the past eight years.

The State Department in Washington having approved of the International Cancer Research Congress, official invitations soon will be sent to all foreign governments who are to send delegates.

Initial steps in the organization of the Congress have been completed, in that all officers and committees have been appointed and are enthusiastically at work. In addition to the President, Dr. E. V. Cowdry, Dr. J. Godard, President of the Union Internationale Contre le Cancer, and Dr. W. U. Gardner, President of the American Association of Cancer Research, will serve ex officio as members of the Executive Committee.

The following men have accepted chairmanships: A. N. Arneson, St. Louis (Local Arrangements); S. Bayne-Jones, New Haven, Conn. (Finance); C. W. Larimore, New York (Exhibits); L. A. Scheele, Bethesda, Md. (Government Liaison); M. G. Seelig, St. Louis (Publicity), and Shields Warren, Boston (Program).

Headquarters will be at the Hotel Jefferson, St. Louis, where some three hundred rooms will be available for guests. Moreover, other nearby hotels in St. Louis have signified a willingness to make reservations on advance notification by those contemplating attendance at the Congress.

American Society for the Study of Sterility.—The third annual convention of the American Society for the Study of Sterility will be held at the Hotel Strand, Atlantic City, N. J., on June 7 and 8, 1947, preceding the annual session of the American Medical Association. The general purpose of the meetings will be to convey to the physicians treating marital infertility an over-all picture of the latest advances in reproduction. The program will include original papers, round table discussions, scientific exhibits and personal demonstrations. The sessions will be open to all members of the medical and allied professions. Additional information may be obtained from the secretary, Dr. John O. Haman, 490 Post Street, San Francisco 2, Calif.

PRESENT STATUS OF THE PROBLEM OF AMEBIASIS

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AND

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MADISON, WIS.

THE PROBLEM of amebiasis is becoming increasingly important to both the medical profession and the public as a result of the experience of physicians in the armed forces and with the return to the United States of men infected with the disease. Some writers have been unimpressed with the magnitude of the problem. In a discussion of problems of tropical diseases in returning military personnel, Meleney [1] stated that malaria and filariasis are of greatest concern. That these two infections constitute a serious problem in public health is widely recognized, but we submit that the number of troops exposed to filariasis in the Pacific was extremely small as compared with the number of those infected with amebiasis. Greene and Fisher [2] expressed the opinion that an increase in amebiasis is unlikely. On the other hand, there are writers who take the opposite point of view. Eusterman [3] stated:

When Johnny comes marching home from tropical and subtropical countries, soldiers with amebiasis, . . . will be seen in increasing numbers by doctors more or less unfamiliar with tropical diseases. Even the larger military establishments are not above occasional error. Recently there came under my observation a young ensign who had been unsuccessfully treated for ulcerative colitis in a naval hospital over a period of 18 months. The frequent bloody discharges made such a diagnosis plausible. But the feces were found to be swarming with Endamoeba histolytica, and intensive treatment fortunately resulted in gradual but complete recovery.

Craig [4] wrote:

At the present time, thousands of our troops are serving in regions where amebiasis is a common and often serious infection, and many of these men will

From the Department of Medicine, University of Wisconsin Medical School.

1. Meleney, H. E.: Problems of Treatment of Tropical Diseases in Returning Military Personnel, New York State J. Med. **44**:2105, 1944.

2. Greene, J. A., and Fisher, W. M.: Tropical Diseases in Texas in the Post War Era, Texas State J. Med. **40**:408, 1944.

3. Eusterman, G. B., in Dick, G. F.: Yearbook of General Medicine, Chicago, Year Book Publishers, Inc., 1945, p. 701.

4. Craig, C. F.: The Etiology, Diagnosis, and Treatment of Amebiasis, Baltimore, Williams & Wilkins Company, 1944.

return to the United States infected with Endamoeba histolytica, the cause of amebiasis. This will add to the already considerable ·percentage of infections with this parasite in this country, conservatively estimated at 10 per cent of the population, and will render the diagnosis and proper treatment of the infection of ·still greater importance from the standpoint of public health.

We subscribe to this view as a result of over three years' experience in the Pacific theater, where we were able to observe some filariasis, the usual amount of malaria and in addition a great many cases of amebiasis. There is sufficient reason for believing that most of the former infections were reported and brought under medical care, so that current estimates of their frequency are fairly complete. With amebiasis, on the contrary, only a small proportion of patients received medical attention, owing to the insidiousness of the infection and the universality of mild diarrhea and intestinal complaints *sufficient* to mask anything short of frank amebic dysentery. A considerable reservoir of unsuspected and unreported amebiasis has undoubtedly been brought back to the United States and civilian life; thus the magnitude of the public health problem created becomes apparent. It would therefore seem appropriate to call attention to the problem as it exists and to emphasize from personal experience certain principles found to be of value in the management of amebiasis.

EPIDEMIOLOGY OF AMEBIASIS

Amebiasis may be defined as infection with the protozoan Endamoeba histolytica, irrespective of the clinical manifestations (or lack of them) presented by the patient. The term includes asymptomatic invasion of the colon (asymptomatic cyst passer, or "carrier"), simple diarrhea, dysentery and hepatic and other extraintestinal infections. It should be emphasized that amebic dysentery and amebic abscess of the liver are not synonymous with amebiasis, for although they are .a part of serious amebic infection they are, in the temperate portion of the United States at least, rarer manifestations of the disease. Were they to be made the criteria of diagnosis, then the vast majority of amebic infections would be entirely overlooked.

There are five common species of parasitic amebas in human beings, of which four are nonpathogenic and acquire importance only by virtue of the diagnostic confusion they create in laboratory identification of the fifth and highly pathogenic species, E. histolytica. Detailed information on morphology may be obtained from standard reference texts.[5]

The parasite has been found wherever surveys have been made in both hemispheres. Although the incidence and severity of infection

5. (*a*) Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 4, Philadelphia, Lea & Febiger, 1945. (*b*) Mackie, T. T.; Hunter, G. W.; and Worth, C. B.: Manual of Tropical Medicine, ed. 1, Prepared Under Auspices of the Division of Medical Sciences of the National Research Council, Philadelphia, W. B. Saunders Company, 1945. (*c*) Craig.[4]

are greater in tropical climates and regions of poor sanitation, the disease occurs in a significant degree elsewhere. For example, in the northern United States, surveys reported from the same clinic over a number of years have shown rates varying from 4.5 per cent to 17.7 per cent, with the average around 12 per cent.[4] In warmer zones the incidence rates have been reported as high as 32 per cent in rural communities and 55 per cent in orphanages.[4] In all probability, the adjusted over-all incidence of infection in the United States as determined to date is in the vicinity of 10 per cent. Rates significantly higher than this have been reported in overseas theaters occupied by American troops.[4]

The life cycle of E. histolytica is simple in that, for practical considerations, only two stages exist. One is the motile, vegetative form, or trophozoite, and the other the nonmotile cyst. The former constitutes the invasive stage responsible for the lesions in the wall of the bowel and other organs and may be found in tissues so infected, on the surface of the intestine or within the lumen. Under the influence of dehydration and possibly other factors unfavorable for the existence of the motile form, encystment occurs in the lumen. With passage of cysts in the feces, transmission of infection is possible. Ingestion of cysts is followed by excystation in the intestine, with invasion in the ileocecal region, and the cycle is completed with the liberation there of new trophozoites.

It is now well established that the trophozoite is not an infectious form of the parasite. Transmission of the disease occurs only after ingestion of cysts, which may be disseminated through the mediums of water, food, flies and direct contact.[6] Indirect proof of the first may be had in the case of the outbreak in Chicago in 1933, in reduction of incidence of disease following installation of sanitary water systems and in certain instances during the recent campaigns in the Pacific, where polluted water afforded the main source of exposure. The medium of food assumes considerable importance in well sanitated region inasmuch as handlers of food may constitute the primary means of spread. This avenue is especially important in familial association, and it should be emphasized that in this situation the cyst-passing veteran will be encountered. Statistics on the incidence of infection in handlers of food are available.[4] Viable cysts have been found in flies caught in dwellings which house human passers of cysts,[7] illustrating the potentialities of this mode of transmission. Finally, direct contact has been

6. Faust, E. C.: Some Modern Conceptions of Amebiasis, Tr. & Stud. Coll. Physicians Philadelphia **11**:101, 1943.

7. Frye, W. W., and Meleney, H. E.: A Survey of Flies, Pigs, Fowls, Rats and Mice in a Rural Community for the Intestinal Protozoa of Man, J. Parasitol. **18**:118, 1931.

shown to be an important method of transmission of infection in orphanages,[8] as well as in hospitals for mental diseases and prisons.

PATHOLOGY OF AMEBIASIS

The pathogenicity of E. histolytica depends on two factors. The first is the ability of the parasite to secrete a potent cytolytic toxin, by means of which dissolution of the intact mucosa of the bowel may be affected. The second is its capacity for active ameboid movement. By a combination of these actions the parasite is capable of invasion of the lining of the entire large bowel, sigmoid, rectum, appendix and distant organs. The sites of predilection in the bowel (infection does occasionally occur in the terminal part of the ileum) are the cecal and rectosigmoid areas and, to a lesser degree, the two flexures, i. e., wherever stasis tends to be the greatest. Of these, the cecum must be recognized as the usual habitat of this organism. The earliest lesions are variable and are said to include pinpoint ulceration, shallow crater-like ulceration or shallow more extensive denudation of mucosa.[9] At this earliest stage the lesions are confined to the mucosa, and, depending on resistance of the host, it is likely that some spontaneous healing occurs. Should healing fail to occur, further penetration of the ulcers follows, with extension through the muscularis mucosa and expansion into the loose submucosa. By this process the classic flask-shaped ulcers result, with typical undermining of edges and sinus formation whenever the submucosal portions coalesce. Further penetration through the outer muscular layers into mesenteric venules and invasion of the portal vein provide the basis for amebic hepatitis or abscess and infection of other organs. Most typical of the gross appearance of the amebic bowel is the discrete nature of the ulcerations, with areas of normal mucosa between them. There is relatively little inflammatory reaction, so that scarring does not follow if the infection is treated early. It should be noted that amebic involvement of the cecum and appendix may masquerade as acute appendicitis with moderate frequency. In our experience, failure to observe this fact has been responsible for a great many unnecessary appendectomies.

THE "CARRIER" STATE

The "carrier" state in amebiasis refers to the asymptomatic passer of cysts. The latter term accurately describes this condition, while the

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8. Ivanhoe, G. L.: Studies in the Transmission of Amebiasis in a Children's Home in New Orleans, Am. J. Trop. Med. 23:401, 1943.

9. (a) James, W. M.: Human Amebiasis Due to Infection with Entamoeba Histolytica, Ann. Trop. Med. 22:201, 1928. (b) Faust, E. C.: Amebiasis in the New Orleans Population as Revealed by Autopsy Examination of Accident Cases, Am. J. Trop. Med. 21:35, 1941.

expression "carrier" is unfortunately misleading. It connotes a situation in which the parasite is assumed to be living within the host as a harmless commensal, not at the expense of the host's tissues, in a manner analogous to a carrier of meningococcus of an avirulent strain, Eberthella typhosa or Corynebacterium diphtheriae. This erroneous belief is engendered by the large percentage (50 per cent) [4] of "carriers" who do not present symptoms of amebic infection. According to this spurious reasoning, since there are no symptoms there must be no pathologic change, and the belief is widespread that E. histolytica may live and multiply within the lumen of the bowel without producing lesions or that an avirulent strain exists. As a result the passer of cysts is lightly regarded and dismissed in a casual manner, when nothing is more unjustified if the facts of the condition be known. Hargreaves [10] has recently expressed this same point of view.

There is abundant evidence in the literature to discredit this belief. Such evidence strongly suggests that infection with the parasite always means invasion of the tissues, with the production of pathologic lesions, and that cysts from asymptomatic "carriers" are fully pathogenic. In 1913 Walker and Sellards,[11] working in Manila, fed to 20 human volunteers the cysts obtained from asymptomatic "carriers." Seventeen of the subjects became infected with parasites, in 4 of whom acute amebic dysentery developed later. Kessel [12] in 1928 showed that amebas from "carriers" are as pathogenic for experimental animals as those obtained from patients with acute dysentery. Spontaneous recovery sometimes occurred, periods of incubation were similar, pathologic lesions were identical and length of life of animals after feeding was the same when results from animals infected from the two sources were compared. Dobell [13] confirmed these conclusions in 1931. Faust,[14] as a result of studies on experimental amebiasis in dogs, stated that there is no detectable difference in susceptibility to human strains of an acute, chronic or carrier type. To date, no nonpathogenic avirulent strains of E. histolytica are known, so that the asymptomatic passer of cysts

10. Hargreaves, W. H.: The Treatment of Amebiasis with Special Reference to Chronic Amebic Dysentery, Quart. J. Med. **15**:1, 1946.

11. Walker, E. L., and Sellards, A. W.: Experimental Entamoebic Dysentery, Philippine J. Sc. (B) **8**:253, 1913.

12. Kessel, J. F.: Amoebiasis in Kittens Infected with Amoebae from Acute and "Carrier" Cases, and with the Tetranucleate Amoebae of the Monkey and of the Pig, Am. J. Hyg. **8**:311, 1928.

13. Dobell, C.: Researches on the Intestinal Protozoa of Monkeys and Man: IV. An Experimental Study of the Histolytica-Like Species of Entamoeba Living Naturally in Macaques, Parasitology **23**:1, 1931.

14. Faust, E. C.: Susceptibility, Resistance and Spontaneous Recovery in Dogs Experimentally Infected with Entamoeba Histolytica, Proc. Soc. Exper. Biol. & Med. **29**:659, 1932.

cannot be dismissed as harboring an avirulent strain. The evidence concerning the parasite's inability to live in the lumen without producing lesions is equally conclusive. Kessel [12] noted that pathologic lesions were present in the intestine in animals free of diarrhea or dysentery for as long as sixty-two days after inoculation. Hegner and others,[15] working with experimental amebiasis in monkeys, reported gross and microscopic lesions with trophozoites in situ in the tissues, without the occurrence of diarrhea. Johnson [16] studied naturally occurring asymptomatic infections in 10 monkeys in Panama. In 9 no gross lesions were observed at autopsy, but microscopic section demonstrated that in 7 of the animals lesions were present containing the trophozoite. Studies on human pathologic material support these experimental observations. Musgrave [17] in 1910 reported 50 cases of persons dying of other diseases, without a history of diarrhea or dysentery or evidence of either in the hospital, who at autopsy had characteristic amebic lesions in the colon. Bartlett [18] in 1917 described 11 cases of patients, without a history of diarrhea before or after their admission to the hospital for wounds and other diseases, who showed extensive amebic ulceration of the intestine at autopsy. Faust [9b] in 1941 reported a study of amebiasis as revealed by autopsy of patients who died of accidents, in whom were found pinpoint ulcerations, shallow crater-like lesions and extensive extremely shallow denudation of mucosa with trophozoites in the lesions in some cases. The lesions noted represent the mildest type of damage to tissue reported in "carriers" and lend support to the belief that E. histolytica lives at the expense of the asymptomatic host. Craig [19] cited other cases of asymptomatic passers of cysts who had amebic ulcerations of the bowel at autopsy. Finally, it is a well known fact that in roughly one third of the cases amebic hepatitis develops in persons who have never experienced diarrhea or dysentery, a fact which strongly suggests that the "carrier" state is a pathologic condition warranting the same serious attention accorded other forms of the disease, since hepatitis is always secondary to invasive lesions of the wall of the bowel.

From the foregoing summary it may be concluded that the bowel of the asymptomatic passer of cysts is the site of pathologic change; that the pathologic change is qualitatively identical with that of amebic

15. Hegner, R.; Johnson, C. M., and Stabler, R. M.: Host-Parasite Relations in Experimental Amoebiasis in Monkeys in Panama, Am. J. Hyg. **15:**394, 1932.

16. Johnson, C. M.: Observations on Natural Infections of Endamoeba Histolytica in Ateles and Rhesus Monkeys, Am. J. Trop. Med. **21:**49, 1941.

17. Musgrave, W. E.: Intestinal Amoebiasis Without Diarrhea. A Study of Fifty Fatal Cases, Philippine J. Sc. (B) **5:**229, 1910.

18. Bartlett, G.: Pathology of Dysentery in Mediterranean Expeditionary Force, 1915, Quart. J. Med. **10:**185, 1917.

19. Craig, C. F.: The Pathology of Amebiasis in Carriers, Am. J. Trop. Med. **12:**285, 1932.

diarrhea or dysentery and differs only quantitatively in tending to be of lesser degree, and that there is no foundation in studies either on animals or on human beings to regard the asymptomatic passer of cysts as a healthy "carrier." A clinical axiom might be drawn by stating that in amebiasis symptoms are not a reliable index of the extent of the pathologic lesions, for the latter may and usually do outstrip the former. We cannot emphasize too strongly our clinical impression that the "carrier" represents an active stage of the disease, often, if not regularly, completely free of symptoms and for this reason the most easily over-looked and neglected. It is the stage of the disease when the opportunity is greatest for prevention of serious and even fatal complications. It is the time when the best chance exists for complete eradication of the infection and for restoration of the patient to full health in the shortest possible time, with the lowest probability of troublesome sequelae. Surely no one would reserve definitive treatment in tuberculosis until cavitation developed. In amebiasis, as in tuberculosis, the time for full and com-plete therapy is as early in the course of the disease as it is possible to give it. This will be, in the vast majority of instances in the United States, in the stage represented by the asymptomatic passer of cysts.

THE MANAGEMENT OF THE PATIENT

An intelligent approach to the management of amebiasis can be made only after the fundamental facts pertaining to the epidemiology and pathology of the disease are understood. These have been reviewed, and special attention has been paid to the so-called carrier state. In discussing the management of the patient with amebiasis, we wish to stress several points: (1) the practical necessity of adopting a complete program of diagnostic procedures to be followed in every case, regardless of the stage of symptomatology; (2) the special problem of hepatitis; (3) the necessity for understanding the requisites of treatment, in view of what is already known about pathology, and the limitations of avail-able drugs, and (4) the recognition of associated conditions, including bacillary dysentery and irritable bowel.

1. *Diagnostic Procedures.*—We believe it is wise to adopt a definite plan for the diagnostic investigation of patients with possible amebiasis, and we suggest that this plan should be followed consecutively in every case, irrespective of the particular phase of the symptomatology. In this way nothing of importance will be overlooked in the establish-ment of the correct etiologic, anatomic and functional diagnosis. A diagnostic program we have found useful is simple and can be applied anywhere. It includes the elicitation of a careful history, physical exami-nation, proctoscopy, examinations of stools and, rarely, roentgenologic examinations.

History.—In approximately 50 per cent of patients there may be no history of intestinal disturbance, in which case cysts may have been discovered on a survey of handlers of food. In other instances a pattern of alternate constipation and diarrhea is important. Patients may recall having mushy semisolid stools three or four times daily for one or two days, followed by normally formed or constipated stools once a day or every other day for several weeks, or the patient may be first interviewed in the midst of a period of watery diarrhea amounting to six to eight stools a day without disturbance of sleep. Rarely, in the United States, will patients be seen with a present history of bloody stools every hour both night and day. The history of the bowel movements can thus vary widely from the cyst passer to the patient with frank dysentery. A parallel variation in intensity may be noted in the elicitation of a history of pain. The patient with the milder condition may well have no cramps. Accompanying a history of alternate constipation and diarrhea usually will be found a story of occasional colicky abdominal cramps referable to the cecum and large bowel, and with histories of severer disorder one finds increasing amounts of pain. Anorexia of mild or severe degree may be the sole or an accompanying symptom of importance. A history of melena is probably the least reliable point in most cases. It is always important to inquire for chills and fever, for in our experience their presence suggests a bacillary infection or, in the case of amebiasis, extension of infection to the liver. Uncomplicated intestinal amebiasis with or without diarrhea seldom accounts for a history of chills and fever. Finally, the possible occurrence of similar symptoms in the patient's family or associates, residence in an area of poor sanitation and a history of overseas service in the Mediterranean, Middle East or Pacific should make one suspicious of amebiasis.

Examination.—Examination may reveal nothing abnormal in the cases of asymptomatic infection, but in cases with alternate constipation and diarrhea it is common to find a boggy-feeling, gas-filled cecum that is sensitive to pressure. In more active infections there is usually tenderness over the course of the large bowel, especially at the flexures, which are sites of predilection. With active dysentery, the sigmoid will show tenderness in addition. The general condition of the patient is usually unaffected by the asymptomatic or mildly symptomatic disorders (hence the appellation "walking diarrhea"). Prostration, dehydration, tachycardia and fever are seen with frank dysentery. It is extremely important in every instance to determine the size of the liver, to note the presence or absence of tenderness if it is palpable and if it is not palpable to carry out gentle percussion over the liver anteriorly and posteriorly in a search for the point of tenderness. The mobility

or fixation of the right leaf of the diaphragm should always be ascertained in the examination. The significance of hepatic findings will be mentioned later. Cecal involvement by E. histolytica may masquerade as acute appendicitis, with pain in the right lower quadrant of the abdomen, tenderness and rigidity, slight elevation of temperature and some increase of the white blood cell count. This puzzling differential diagnosis was encountered with significant frequency in highly endemic areas during the war. Urinalysis and blood cell counts may be made as a part of the initial examination, but in our experience the results are within normal limits in uncomplicated intestinal amebiasis. Our experience substantiates the general belief that eosinophilia is not a manifestation of amebiasis, and its occurrence indicates the probable coexistence of helminthiasis.

Proctoscopy.—Proctoscopy should be a part of the initial study in every case of amebiasis, as it can provide invaluable information. Of special importance in this connection are color of the mucosa and the presence of bleeding points, pus, mucus, edematous areas and ulcerations. Often in asymptomatic patients the rectosigmoid will be normal in appearance, so that such an observation does not invalidate the etiologic diagnosis. Some patients, on the other hand, will be found to have scattered pinpoint ulcers when least expected, thus emphasizing the importance of proctoscopy. A typical early appearance indicative of the condition consists of scattered discrete ulcers, of whitish color, somewhat oval in shape, 1 to 2 mm. in length, situated with the long axis in the transverse axis of the bowel and surrounded by a bright red areola 2 to 3 mm in width, with large areas of perfectly normal mucous membrane between and around them. We have observed mild conditions in which not more than one or two such tiny ulcers could be found after careful search. The location of the ulcers should be noted for future comparison. In severe diarrhea or dysentery the number of such ulcers increases, bleeding from them will be seen and the areas of uninvolved normal mucosa are less prominent. Observation of the foregoing picture is practically conclusive of amebic infection, but final diagnosis must await identification of the parasite. Following examination of the bowel, specimens are taken for laboratory examination. It is usually sufficient to collect several swabs of ulcerated areas, mucus or fecal material in a few cubic centimeters of warmed isotonic solution of sodium chloride, which can be taken to the laboratory directly without cooling. Ideally, the microscopic examination should be made at the proctoscopic table.

Examination of Stools.—Proctoscopic material is examined with exactly the same technic as that used for passed specimens, which may

be obtained if proctoscopic material fails to yield trophozoites or cysts. At least three daily naturally passed stools and one following administration of sodium sulfate or phosphate should be examined. A direct warm preparation in isotonic solution of sodium chloride should be searched for the motile trophozoites; a direct preparation in isotonic solution of sodium chloride or fecal preparation should be stained with a drop of D'Antoni's iodine (1.5 Gm. of powdered iodine crystals in 100 cc. of 1 per cent potassium iodide solution) and searched for cysts, and a third sample should be concentrated by the zinc sulfate method and then searched for cysts. These three technics should be employed on each sample taken to the laboratory. Details of laboratory technic are available in the manual of Mackie and others.[5b] In general, one expects to find cysts in a formed specimen and trophozoites or cysts in a diarrheic liquid specimen. Use of a bismuth preparation as a means of symptomatic treatment of diarrhea and the use of barium sulfate for roentgenologic study should be avoided at this point in the investigation, as they may prevent the demonstration of cysts for at least ten days after administration.

Roentgenologic Examination.—Roentgenologic examination is indicated in the diagnosis of hepatitis and is helpful in the study of irritable or scarred bowel. It is of no value in the early investigation of intestinal amebiasis. It is our belief that every case of amebiasis should be approached in some such orderly logical sequence in order to obtain the best results. For example, much time and expense will be saved by proctoscopy after the physical examination, for if proctoscopic material is found to contain the parasite, three or four days of repeated examination of stools may be eliminated entirely, and treatment may be started at once. If ulcers are found, one has an accurate base line by which to judge the effect of therapy with post-treatment proctoscopy, and if the mucosa is normal further proctoscopy is unnecessary.

2. *Hepatitis.*—Hepatitis poses a special problem, which can only be touched on here. It is important to remember that in at least 33 per cent of cases it develops in asymptomatic passers of cysts and in one series [20] it is reported a history of diarrhea or dysentery was obtained in only 32.7 per cent of cases of amebic abscess of the liver, i· e., in possibly two thirds of the cases the condition occurred in previously asymptomatic subjects. Thus the presence of diarrhea is helpful, but its absence means nothing. However, in the diagnosis of hepatitis the presence of E. histolytica in the stools is corroborative. Other signs and symptoms include spiking fever; chills; pain, which may be in the

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20. Sodeman, W. A., and Lewis, B. O.: Amebic Hepatitis, Am. J. Trop. Med. **25**:35, 1945.

right upper quadrant of the abdomen, posteriorly over the liver or along the ridge of the trapezius muscle and related to respiration; nausea, anorexia and vomiting; tender liver on palpation or percussion; leukocytosis ranging from 12,000 to 30,000 cells, with increase in segmented neutrophils, and, finally, changes in the right leaf of the diaphragm. Roentgenologic examination is helpful in showing an elevation and fixation if roentgenograms are taken on both inspiration and expiration, and pleural effusion of the right lung can often be demonstrated. The absence of jaundice is helpful in distinguishing amebic from epidemic infectious hepatitis. In some instances diagnosis can be established only by observation of the response of the patient to a course of emetine hydrochloride. The treatment of amebic hepatitis is conveniently considered here. It consists of a full course of emetine hydrochloride, amounting to 10 grains (0.65 Gm.), with full courses of either carbarsone, chiniofon or diodoquin. Small abscesses probably respond to this therapy, while larger, well established abscesses require aspiration. The reader is referred to a recent paper by Ochsner [21] for a consideration of the surgical aspects of amebic abscess of the liver. It is important to remember that early diagnosis of amebic hepatitis permits cure by medical means alone. In addition to specific therapy, there are general supportive measures which are important in the management of extremely ill patients with amebic hepatitis. These include administration of sufficient plasma or albumin to maintain normal serum protein levels when anorexia and damage to the liver threaten the level of circulating protein and parenteral administration of dextrose in isotonic solution of sodium chloride to spare body protein and maintain a satisfactory balance of fluid and urinary output. The following cases are presented to illustrate two of the specific problems encountered in amebic hepatitis.

CASE 1.—An officer in the air corps, with a few months' tropical service, without history of diarrhea and dysentery, was well until one day before entry to the hospital, when he noted malaise, anorexia and feverishness. On the day of entry he complained of sudden onset of cough, dyspnea and pain in the right lower part of the chest anteriorly and laterally. Examination revealed an acutely ill dyspneic man with grunting respiration and splinting of the right lower part of the chest. The percussion note was resonant, breath sounds were transmitted and no rales or rub was heard over the right side of the chest. Considerable resistance was felt on palpation of the right upper quadrant of the abdomen, but it was impossible to feel the liver. Percussion over the right anterolateral costal margin was slightly painful. There was a leukocytosis of 12,000, with a normal differential count, while the rest of the laboratory work was noncontributory. A roentgenogram of the chest was normal. The first specimens of stool were

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21. Ochsner, A., and DeBakey, M.: Surgical Amebiasis, Internat. Clin. **1**:68, 1942.

negative for E. histolytica. He had a septic course, with evening chilling and temperature of 102 to 104 F. and a fall in the morning to 99 and 100 F. He continued to complain of anorexia, dyspnea and pain in the right anterolateral costal margin. Pain developed along the ridge of the right trapezius muscle, the liver became definitely palpable in a few days and a second roentgenogram of the chest showed elevation of the right side of the diaphragm, without bulging. A specimen of the stool examined after a purge was positive for cysts of E. histolytica. Administration of emetine hydrochloride (1 grain [60 mg.] intramuscularly daily) was started, and this dose was continued for ten days. He was comfortable after the first two or three doses and became afebrile in four to five days. The tenderness on percussion was absent at the end of treatment. Chiniofon (0.5 Gm. three times a day) was given for ten days and followed by administration of carbarsone (0.25 Gm. twice daily) for ten days. He was ambulatory and feeling fine when transferred to another hospital for convalescence.

Comment.—This is an instance of how amebic hepatitis can provide a puzzling diagnostic problem when it appears in an apparently well person who has not had diarrhea or intestinal complaints previously. While the presenting symptoms suggested acute pleurisy, the absence of signs related to the chest and the presence of tenderness on percussion over the liver pointed to the correct diagnosis. The roentgenogram was helpful, the amebas in the stool were corroborative and the therapeutic response to emetine hydrochloride clinched the diagnosis.

CASE 2.—In a soldier who had served under extremely poor conditions in the southern Philippines for many months, watery diarrhea developed about two weeks before entry. He was given nonspecific therapy on sick call and became constipated. He took a purgative for this, following which severe diarrhea, cramps and tenesmus ensued. He was admitted to a hospital, where E. histolytica was reported in the stools and treatment begun with diodoquin. This failed to control the diarrhea. Emetine hydrochloride (1 grain [60 mg.] intramuscularly daily) was given for three days, with lessening of diarrhea. However, chills, temperature of 103 F. and pain in the right upper quadrant developed. A diagnosis of amebic abscess of the liver was considered, but administration of emetine hydrochloride was discontinued and the patient transferred to another hospital. On entry, he was in severe pain, acutely ill and appeared dehydrated and debilitated. The temperature was 103 F. The most important finding was an exquisitely tender liver enlarged downward 15 cm., with accompanying painful hyperesthesia of the overlying skin. There was a leukocytosis of 25,000, and the roentgenogram of the chest showed elevation and fixation of the right side of the diaphragm. Emetine hydrochloride therapy (60 mg. daily) was resumed, and it was continued for seven days, making a total of 10 grains (0.6 Gm.) received in the two hospitals. During this week he was unable to eat or retain liquids, mild icterus developed, hypoproteinemia with edema of the ankles appeared and mild circulatory collapse was evident. He was given two transfusions of whole blood and repeated injections of plasma, dextrose and isotonic solution of sodium chloride, and he was able to retain fluids and food by mouth. By the end of the course of emetine hydrochloride the pain and tenderness of the liver had disappeared completely, but the fever continued irregularly, the temperature occasionally reaching 103 F. in the evening and at other times remaining around 99 F. Cough and sputum and rales over the lower fields of both lungs developed. A roentgenogram of the chest revealed four round discrete areas of increased density suggestive of early abscess formation, two in each lower lobe. There were no signs of infiltra-

tion above the right side of the diaphragm to suggest direct spread from a sub-diaphragmatic source. It seemed unlikely that he had pulmonary abscess from amebiasis, since he had just completed one course of emetine hydrochloride. Sulfadiazine therapy was given for one week, without effect. The danger of toxicity involved being recognized, it was decided to give another course of emetine hydrochloride to see whether any effect could be obtained on the pulmonary process. Administration of another 7 grains (0.42 Gm.), given in doses of 60 mg. daily, had no effect. Administration of penicillin was resorted to, and in four weeks the roentgenogram of the chest was normal, the sputum and cough ceased, the temperature became normal and decided subjective improvement was made. In the meantime, a ten day course of chiniofon and carbarsone had been given and the stools became negative for E. histolytica. The patient was transferred to the United States because of prolonged hospitalization.

Comment.—In contrast to the first case, the diagnosis presented no difficulty, as the hepatitis developed in the presence of a recognized amebic diarrhea. The case provided an almost overwhelming therapeutic problem because of the degree of failure of the liver and inanition accompanying the amebic hepatitis. Administration of emetine hydrochloride plus supplementary protein, dextrose and fluids seemed to rectify the situation. The cause of the pulmonary complication was unexplained, although the therapeutic response is against an amebic origin (resistant to 17 grains [1.10 Gm.] of emetine hydrochloride) and favors a bacterial origin.

3. *Requisites of Treatment.*—It is the aim of specific therapy to eradicate all parasites from the host. To do this, one must take into account pathologic changes of the disease and limitations of the available drugs. From the section on the "carrier" state, it is clear that invasion of the tissue by the amebas must be expected in every case of amebiasis. Perhaps this concept is not capable of proof in every instance; yet when the clinician considers the individual case before him there is no way for him to say that this is the one in which invasion of the tissues has not occurred. Hence, the logical course is to expect invasion in all cases and plan therapy with this in mind. It is now possible to divide the infecting parasites into two groups according to location. The first comprises the trophozoites within the tissues, whether the mucosa, submucosa or muscularis of the colon, the mesenteric venules or liver or other areas. The second comprises both trophozoites and cysts outside of the tissues, i. e., in the lumen admixed with fecal material or on the surface of the bowel. Rational therapy must be planned to reach and destroy parasites in both groups. At this point it is necessary to take into account the limitations of the available drugs. Emetine hydrochloride given parenterally acts solely on trophozoites within the tissues, i. e., the first group, and there it is extremely efficient, as witnessed by the dramatic response of hepatitis or severe dysenteric symptoms to its administration. It leaves relatively untouched, however, the trophozoites and cysts outside the tissues, i. e., the second group, in the lumen or

on the surface of the bowel. For this reason it will not eradicate amebiasis, for unharmed trophozoites will continue to invade, and cysts will undergo excystation, and after a period of remission symptoms will return. Emetine hydrochloride is therefore of proved efficacy against the amebas only after they have invaded the tissues. The enteric drugs, such as chiniofon, diodoquin, vioform and carbarsone, act on trophozoites and cysts of the second group, within the lumen of the bowel. There they are efficient, just as emetine hydrochloride is within its sphere. What effect, if any, they may have on trophozoites which have already invaded the tissues is an open question. There is a common assumption that these drugs do reach them, but it is an assumption and not based on fact. We do not know of any instances in which amebic hepatitis has responded to chiniofon or carbarsone. Nor do we know of any studies which demonstrate that any of these drugs are absorbed in therapeutic concentrations· Chen[22] demonstrated that arsenic could be recovered from the urine in small amounts after ingestion of carbarsone (a total of 8 per cent of administered arsenic after fifty-two hours in 1 subject and 13 per cent after forty-two hours in the other), but it is unjustifiable to assume that excretion of elemental arsenic proves the absorption of carbarsone. It is true that David[23] and his co-workers showed that an increase in blood iodine occurred after administration of vioform and diodoquin, but this does not prove that the iodine measured was still bound in the compounds fed, an extremely important point. We maintain that it remains to be shown that they are effective on trophozoites actually within the tissues. It may be seen that emetine hydrochloride and the enteric drugs are complementary, one having its action on parasites within the tissues and the other on parasites within the lumen of the bowel. Knowing this and taking into account the invasion of the tissues and resultant separation of the organisms into two groups, it is possible to recommend therapy logically designed to eradicate all parasites from the host.

Complete amebicidal therapy ought to include use of both emetine hydrochloride and one or more enteric drugs if the maximum degree of effective protection of the patient is to be attained. This statement we believe to be equally true for all forms of amebiasis, regardless of the phase of symptomatology. It is realized that this represents a departure from opinion expressed in· the ·textbooks,[24] in which one finds the

22. Chen, M.; Anderson, H. N., and Leake, C. D.: Rate of Urinary Arsenic Excretion After Giving Acetarsone and Carbarsone by Mouth, Proc. Soc. Exper. Biol. & Med. **28**:145, 1930.

23. David, N. A.; Phatak, N. M., and Zener, F. B.: Iodochlorhydroxyquinoline and Diiodohydroxyquinoline: Animal Toxicity and Absorption in Man, Am. J. Trop. Med. **24**:29, 1944.

24. Craig.[4] Craig and Faust.[5a]

recommendation to use an enteric drug alone in the treatment of the "carrier" and of mild amebic diarrhea, reserving emetine hydrochloride for control of dysenteric symptoms and hepatitis. Nevertheless, it is believed that a critical appraisal of the pathologic changes of the infection and the characteristics of the drugs supports our view.

For the treatment of the asymptomatic passer of cysts and the patient with mild diarrhea it is suggested that emetine hydrochloride be given in total amounts of 5 or 6 grains (0.3 or 0.36 Gm.) in divided doses of 1 grain (0.060 Gm.) daily. This should be sufficient to destroy the trophozoites that have invaded the intestinal wall and that must be reached via the blood stream. For the treatment of more massive invasions, such as acute dysentery and hepatitis, larger doses of emetine hydrochloride up to the full 10 grains (0.6 Gm.), are indicated. These total dosages are for persons weighing about 150 pounds (68 Kg.). While heavier persons should not ordinarily receive more, it is advisable in the case of much lighter subjects to reduce the total dosage on an approximate basis of 10 mg. per kilogram. The amount corresponding to 10 grains (0.64 Gm.) is then given over ten days' time, and that corresponding to 5 grains (0.32 Gm.) is given over five days. Under extreme necessity, a short course of emetine hydrochloride may be repeated after a rest period of ten days, provided strict precautions are observed and administration of the drug is discontinued at the earliest sign of toxicity. Certain care is necessary in the use of emetine hydrochloride. The patient must be asked to stay in bed from the third day of therapy to the second day after its completion. Bathroom privileges should not be allowed. It is wiser to write the order for one day's dose at a time, in order to avoid the chance for medication to be inadvertently continued as a part of routine nursing orders. The pulse rate and blood pressure should be measured daily, and electrocardiograms, if available, usually give additional valuable information. The patient should be seen daily while receiving emetine hydrochloride and examined by the physician, care being taken to note any irregularity of pulse, and inquiry should be made as to any soreness of the muscles, especially in the scapular regions. Use of the drug should be stopped if reasonable belief exists that appearance of extrasystoles or tenderness of the muscles is due to the therapy. (The toxic action of emetine hydrochloride is chiefly on cardiac and striated muscle. It is excreted extremely slowly, so that six to eight weeks are probably necessary for total elimination.) The use of the enteric drugs is uniform regardless of the phase of the infection. They are given until repeated examination of the stools fails to show the presence of trophozoites or cysts. Chiniofon is used in dosages of 0.5 to 0.75 Gm. three times a day, given after meals, for ten days. It is stated that one course will eliminate 90 per cent of infections as deter-

mined by examination of the stool. A second course will almost always be sufficient. Side effects include a sensation of rectal burning or itching and mild to violent diarrhea. The latter is believed to be helpful in sweeping parasites out of the bowel but can be regulated by adjusting the dosage or by the use of camphorated tincture of opium so that one or two loose stools a day result. Diodoquin has been recommended by D'Antoni [25] in doses of 0.6 Gm. three times a day for twenty days. He reported a 95 per cent cure with one course of treatment with this drug. It is believed to be as safe as chiniofon and less apt to produce uncomfortable side reactions. Carbarsone, the best of the arsenical preparations, is used in dosages of 0.25 Gm. twice a day, after meals, for ten days. One course will eliminate from 85 to 95 per cent of infection. Side effects are occasional headache and light headedness. It should not be used in the presence of known sensitivity to arsenic (dermatitis and optic atrophy). We have not encountered any intolerance to it in cases of epidemic infectious hepatitis, although the statement is made that it should not be given in the presence of hepatic disease. The usual plan of treatment is to start the patient on a course of carbarsone and follow with one of chiniofon, or vice versa, as by this method no rest period need intervene between courses. An alternate method is to give one twenty day course of diodoquin. The first course is given concurrently with the emetine hydrochloride, as time is saved and no harmful effects have been observed. After use of emetine hydrochloride is discontinued the patient may be treated while ambulatory if symptoms warrant it. Following completion of enteric treatment three daily examinations of the stools are done. If they are positive for parasites, another course of enteric treatment is given, but if sterile, it is desirable to recheck on approximately the fifteenth, sixteenth and seventeenth days after completion of treatment before the patient is dismissed as cured. An adequate follow-up consists of a monthly check of the stools for three months and then every three months for nine months, or a total of one year. It is desirable to have the periodic examination of the stools made of a purge specimen, as this will give the highest percentage of specimens positive for parasites with the least expenditure of time and expense. (It detects at least 75 per cent of cases which might be ultimately discovered, as high a percentage as can be revealed by examining six consecutive normally passed stools.[26])

A divergence of opinion still exists relative to the best drug to use in the treatment of amebiasis. British authorities have usually favored

25. D'Antoni, J.: Further Observations on Amebic and Bacillary Colitis in the New Orleans Area, Am. J. Trop. Med. **23**:237, 1943.

26. Andrews, J.: The Diagnosis of Intestinal Protozoa from Purged and Normally Passed Stools, J. Parasitol. **20**:253, 1934.

the use of emetine and bismuth iodide given orally in doses of 3 grains (0.18 Gm.) as a loose powder in gelatin capsules each night for twelve consecutive days. Hargreaves has written an excellent summary of this point of view.[10] American physicians in general have employed emetine hydrochloride given by intramuscular injection in doses of 1 grain (0.060 Gm.) for eight to ten consecutive days. Since no directly comparative study is available to settle the relative efficacy of these two preparations, it is not possible to resolve this question. The latter method has the possible advantage of insuring absorption of the entire dose and delivery of that amount to the tissues invaded by the organism. On the other hand, its efficacy in curing amebic dysentery has been estimated not to exceed 25 per cent, but when used in conjunction with chiniofon to attack the organisms in the intestinal lumen this therapeutic efficiency is greatly enhanced and, in the opinion of many, exceeds the effectiveness of emetine and bismuth iodide.[27]

Hargreaves [10] has made a valuable contribution to the treatment of chronic intestinal amebiasis through the use of the sulfonamide drugs and penicillin as preparatory medication to the use of the amebicidal drugs, in order to combat the secondary bacterial invaders which often complicate enteric infections, most of which are sensitive to one or the other of these preparations. The results he reported from the use of this plan of therapy are brilliant and justify unqualified recommendation of these accessory drugs, especially in chronic conditions which are likely to be unusually resistant to treatment.

Nonspecific treatment in intestinal amebiasis will probably be necessary in cases of dysentery or severe diarrhea. Rest in bed and a low roughage diet are the two most important considerations. For severe cramps, the use of 0.032 Gm. of phenobarbital and 0.032 Gm. of codeine every four hours as needed is valuable. If dehydration is a problem, it is best corrected by use of isotonic solution of sodium chloride intravenously.

4. *Associated Conditions.*—Recognition of such conditions is frequently of importance in the care of a patient with amebiasis. Two of these will be discussed, the first of which is bacillary dysentery. This is apt to cause confusion should the patient present himself while having frequent loose stools. The distinction may usually be made on proctoscopic examination when in the case of bacillary dysentery the mucosa is uniformly involved. There are no normal areas spared as in amebiasis. The bacillary process is one of more or less intense erythema, edema, possibly many small bleeding abrasions and much mucopurulent exudate on the surface. Microscopic examination of

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27. Faust, E. C.: Personal communication to the authors, 1946.

the exudate in suspensions of isotonic solution of sodium chloride reveals pus cells in large numbers, whereas in amebiasis one sees only an occasional monocyte or a few red cells. A culture planted at the time of proctoscopy, if the appearance suggests bacillary infection, is a third means of differentiating the two conditions. If these diagnostic criteria are present and sulfonamide therapy is given, the response will help to decide the cause of the dysentery. Approximately 10 per cent of the patients with amebiasis in our experience have had associated bacillary dysentery. It must be remembered that the asymptomatic passer of cysts may have a superimposed Shigella infection which brings him to the physician or that, following such an infection, a previously unsuspected amebiasis may become clinically active. The latter point should be recalled before failure of treatment is admitted or before a diagnosis of chronic bacillary dysentery is made. The second condition frequently associated with amebiasis, or perhaps oftener following it, is the irritable bowel. The patients with this syndrome do not have cysts in their stools, and so far as can be determined they are cured of their infection. They complain of crampy abdominal pain, usually not well localized, generally coming after meals and nearly always made worse by foods of high bulk, e.g., string beans, cabbage, whole tomatoes and dry cereals. They will also note some irregularity of bowel habits, varying from looseness to constipation. Frequently they resort to laxatives, which adds to the difficulty. On examination they may have borborygmi, sometimes tenderness over the colon and signs of an unstable autonomic nervous system. Proctoscopy is noncontributory. Barium enema usually shows an increased motility of the colon, with spasm and decreased emptying time, conditions which may be produced occasionally by the administration of castor oil in preparation for roentgenologic examination, which is a point to consider in ordering roentgenograms of such patients or in their interpretation. This syndrome is especially liable to follow a long-standing amebic infection of the bowel and is not common in patients treated early. The condition is not per se a basis for diagnosis of psychoneurosis. It may persist for several months. The treatment of most value is the insistence on a low roughage diet, the strict avoidance of tobacco and all laxatives, the use of liquid petrolatum at bedtime if needed for obstipation and use of belladonna or occasionally codeine or phenobarbital in doses of 0.032 Gm. each for cramps.

SUMMARY

Attention is directed to the problem of amebiasis. From personal experience emphasis is laid on certain principles found to be of practical value in the management of this condition. The salient facts concerning the epidemiology and pathology of this infection are briefly

reviewed, and the epidemiologic importance of cyst-passing veterans is emphasized. The so-called carrier state is discussed, and evidence is presented to show that there is no such condition as a healthy "carrier" of amebiasis. Rather, the asymptomatic passer of cysts must be considered to be in an active stage of the disease, a fact of utmost importance to the health of the person and of the public. The management of patients embraces at least four considerations: 1. A diagnostic program is outlined in detail. 2. The special problem of hepatitis is illustrated with histories of 2 cases. 3. The question of specific therapy is discussed and a rational basis presented for the use of both emetine hydrochloride and enteric drugs in every case of amebiasis, regardless of symptomatology. 4. The differential diagnosis and treatment of the two most commonly associated conditions, bacillary dysentery and irritable bowel, are discussed.

HEMOLYTIC STREPTOCOCCIC SORE THROAT

The Course of the Acute Disease

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THE INITIAL phase of acute sore throat caused by group A hemolytic streptococci in young men has been previously described elsewhere.[1] Special attention was paid to the symptoms, signs and results of clinicopathologic and bacteriologic studies. Exudative tonsillitis was a frequent manifestation of streptococcic respiratory disease, but this sign was absent in many cases. Edema of the pharyngeal tissues and tender adenitis in the anterior cervical region were emphasized as abnormalities which were of value in the recognition of infection by hemolytic streptococci. Atypical cases were described, in which no definite evidence of streptococcic infection could be obtained by clinical study in the absence of serial antibody determinations. A cutaneous rash was associated with streptococcic sore throat in only a few cases.

This paper has been prepared for the purpose of recounting the subsequent events which occurred in this group of patients during the initial phase of the disease and the suppurative complications that followed. Certain bacteriologic and clinicopathologic information that was obtained will also be described. The nonsuppurative disorders that were often initiated by infection with hemolytic streptococci and the

1. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic and Nonstreptococcic Diseases of the Respiratory Tract: A Comparative Clinical Study, Arch. Int. Med. **78**:369 (Oct.) 1946.

immunologic phenomena that were observed will be considered in other papers.[2]

METHODS

The methods used and the nature of the group studied have been described.[1] Patients admitted to a large station hospital and believed, on clinical and bacteriologic grounds, to be suffering from acute respiratory infection caused by group A hemolytic streptococci were accepted for detailed consideration. Frequent clinical examinations were carried out over a period of ten days in the hospital, and the men were seen again in follow-up at the end of the third week of illness. Many were observed more frequently and for longer periods. The throat and nose were repeatedly swabbed while the patient was hospitalized and again on follow-up. Swabs were streaked on the surface of mule blood agar plates and the isolated hemolytic streptococci classified into groups and types by the precipitin technics of Lancefield.[3] Total leukocyte counts were done on approximately the second and tenth days of illness and erythrocyte sedimentation rates (Westergren) on the second, tenth and twenty-first days. Serial determinations of the antistreptolysin and antifibrinolysin titers of the serum or plasma were often carried out.[4]

Four hundred and ten men were originally included in the group of cases believed to be examples of infection by group A hemolytic streptococci. Serial antibody determinations were made in 342, and a significant response[5] was discovered in 300. The latter may be regarded as proved cases of hemolytic streptococcic disease. This report will be based on an analysis of the records of these 342 cases and particularly of 299 in which detailed clinical and laboratory data were available and in which a complete follow-up examination was made.

SEROLOGIC TYPES

A total of twenty-six different serologic types of group A hemolytic streptococci were isolated from patients in the study group, of which only six (types 3, 17, 19, 30, 36 and 46) were each responsible for 15 or more cases. The natural history of the disease process caused by these six types has been analyzed, although the number of persons in each group is small, since the detailed information obtained during this study has not been previously available and because the organisms of the six types differed in regard to certain biologic characteristics.

2. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: (a) Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131 (Sept.) 1945; (b) Hemolytic Streptococcus Sore Throat: The Poststreptococcic State, Arch. Int. Med., to be published; (c) Hemolytic Streptococcus Sore Throat: Immunologic Observations, to be published.

3. Lancefield, R. C.: Specific Relationship of Cell Composition to Biological. Activity of Hemolytic Streptococci, in Harvey Lectures, 1940-1941, Baltimore, Williams & Wilkins Company, 1941, vol. 36, p. 251.

4. (a) Rantz, L. A., and Randall, E.: A Modification of the Technique for Determination of the Antistreptolysin Titer, Proc. Soc. Exper. Biol. & Med. **59**:22, 1945. (b) Boisvert, P. J.: The Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**:65, 1940.

5. A "significant response" was defined elsewhere.[1]

Infection by types 17 (28 cases), 19 (42 cases) and 30 (20 cases) was similar in that a moderate antistreptolysin response was regularly stimulated and that an increase in antifibrinolysin occurred in approximately half of all cases. A scarlatiniform rash appeared in nearly all persons with a positive reaction to the Dick test, and reactivity of the skin to Dick toxin was lost during convalescence. Infections by type 3 (33 cases) were followed by a much greater increment of antistreptolysin and a much less frequent antifibrinolysin response than those just described. Furthermore, a cutaneous rash was observed in only 1 case, but reaction to the Dick test of the skin regularly became negative during convalescence.

Infection by types 36 (58 cases) and 46 (15 cases) was never associated with a rash or reversal of the Dick reaction. The antistreptolysin response was comparable in both groups, but disease caused by type 46 was almost always followed by a sharp increase in antifibrinolysin whereas that caused by type 36 usually was not. The full evidence on which these statements are based will be presented elsewhere.[2c]

<div align="center">THERAPY</div>

One of the following therapeutic regimens was instituted in each case on the first or second day in the hospital. Their effect on the course of the disease has been presented [6] but will be briefly reevaluated here.

Symptomatic.—Patients receiving only symptomatic therapy gargled frequently with hot solution of sodium chloride and received codeine as necessary for the relief of pain and discomfort. No salicylates or antibacterial agents were administered.

Sulfadiazine.—Four grams of sulfadiazine was administered by mouth as an initial dose, followed by 1 Gm. every four hours day and night. The average total dose for the group was 39 Gm. and the duration of therapy six and a half days.

Salicylates.—Ten grams of sodium salicylate was administered by mouth each day for approximately one week.

Penicillin Followed by Sulfadiazine.—Two hundred thousand units of penicillin was administered intramuscularly in eighteen to twenty-four hours, the individual injections being given at intervals of four hours. A standard oral course of sulfadiazine was begun with the last dose of penicillin, an average of 33 Gm. being given in five and four-fifths days.

6. Spink, W. W.; Rantz, L. A.; Boisvert, P. J., and Coggeshall, H.: Sulfadiazine and Penicillin for Hemolytic Streptococcus Infections of the Upper Respiratory Tract: An Evaluation in Tonsillitis, Nasopharyngitis, and Scarlet Fever, Arch. Int. Med. **77**:260 (March) 1946.

Penicillin (Short Course).—Two hundred thousand to 400,000 units of penicillin was administered intramuscularly in divided doses at four hour intervals in from thirty-two to sixty-four hours.

Penicillin (Long Course).—Five hundred thousand or 1,000,000 units of penicillin was administered intramuscularly in divided doses at four hour intervals in eighty hours.

The hemolytic streptococci isolated from many patients who had received a sulfonamide compound or penicillin were tested to determine the sensitivity of the organisms to these agents.[7] Thirty-two strains, recovered from men in whom sulfadiazine had been utilized alone, were studied. Five were resistant to 1 mg. and twelve to 5 mg. of sulfadiazine per cubic centimeter. Twenty-six strains obtained from as many patients in the group receiving penicillin followed by sulfadiazine were similarly tested. Eight grew in the presence of 1 mg. and eight in 5 mg. per cubic centimeter of sulfadiazine. Strains were available in 75 per cent of the cases in which penicillin had been administered. All were inhibited by 0.05 unit per cubic centimeter or less of this chemical.

For the purpose of certain comparisons, the number of cases in each category became too few if the treatment groups were subdivided on the basis of the sensitivity of the etiologic agents to sulfonamide drugs. All cases in which a sulfonamide compound was administered therapeutically, either alone or preceded by penicillin, were tabulated together. One group (33 cases) was established in which the isolated hemolytic streptococcus grew in 1 or 5 mg. of sulfadiazine per cubic centimeter, and another (25 cases) was established in which the organisms were completely inhibited by the smaller amount of the drug.

CLINICAL OBSERVATIONS

The clinical manifestations of the initial phase of acute sore throat caused by group A hemolytic streptococci have been presented elsewhere [1] and will not be recapitulated.

The infectious process caused by each of the six previously described types of hemolytic streptococci has been compared with regard to the frequency of occurrence and the severity of sore throat, headache, generalized aching, coryza, chills, hoarseness, pharyngeal exudate, edema, redness, tender adenitis of the anterior cervical region and cutaneous rash. A scarlatiniform rash occurred only in association with infection by types 3, 17, 19 or 30. No other significant [8] differences were dis-

7. Wilson, A. T.: Method for Testing in Vitro Resistance of Group A Hemolytic Streptococci to Sulfonamides, Proc. Soc. Exper. Biol. & Med. **58**:130, 1945.

8. The various percentages were compared throughout by a simplified method devised by Professor Holbrook Working, of Stanford University, for the determination of the approximate standard deviations of fractions. Differences greater than twice the standard deviation of the mean were required as an index of significance.

covered in the initial clinical manifestations of the disease caused by these serologic types of hemolytic streptococci.

The course of the disease has not been previously described and will now be considered.

Maximum Temperature.—Fever was noted during the period of hospitalization of nearly all these men, since afebrile patients were not admitted to the section of the hospital for patients with respiratory disease. The relationship of the maximum recorded temperature to a number of features of hemolytic streptococcic sore throat is portrayed in table 1. A rise in temperature to 102 F. or more occurred in 63.3 per cent and to 103 F. or more in 40.0 per cent of 300 proved cases. Low grade fever was uncommon, only 6.6 per cent of these patients having constantly maintained a temperature of less than 100 F. The presence of an antibody response, tonsils or cutaneous rash had no significant effect on the height of the temperature, nor did the amount of exudate present in the throat. Absence of tender cervical adenitis was associated with significantly less febrile illness.

Infection by types 3, 17, 19, 30, 36 and 46 resulted in a comparable range of maximum temperatures. The data on which this statement is based have been omitted.

Duration of Fever.—The duration of fever will be treated in a similar manner. The essential data are included in table 2. Seventy-one per cent of the patients with proved streptococcic infection were afebrile within three days and 85.7 per cent within four days. The presence or absence of tonsils or of an antibody response did not alter these values. Patients in whom a cutaneous rash was observed were febrile for a much longer time, an elevated temperature having been noted for five or more days in 48.1 per cent of this group. Neither the severity of tender cervical adenitis nor the amount of exudate in the throat could be correlated with the length of the febrile illness.

The type of Streptococcus affected the duration of fever, since infection by types 17, 19 or 30 was accompanied with a more prolonged (five or more days) febrile course than was that caused by types 3, 36 and 46. Analysis of the data reveals that this was the result of the inclusion of many patients with rash in the first three groups.

The last section of table 2 reveals that the duration of fever was longer in patients treated with various antibacterial agents than in the group as a whole. The relatively higher initial leukocyte counts (table 6) and the large number of instances of cutaneous rash (18 cases) in treated patients indicate that these were more severely ill and explains in part the prolonged febrile illness in these persons. In 5 cases, a relapse, following inadequate penicillin therapy, was the cause of prolonged initial fever. Cases will be mentioned later in which this phenomenon occurred, but they are not considered here because the tempera-

TABLE 1.—*Maximum Temperatures in Hemolytic Streptococcic Sore Throat*

	No. of Cases	Afebrile		99 to 99.9 F.		100 to 100.9 F.		101 to 101.9 F.		102 to 102.9 F.		103 F. and Over	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Antibody response	300	7	2.3	13	4.3	31	10.3	59	19.6	70	23.3	120	40.0
No antibody response	42	0	0.0	3	7.1	7	16.7	9	21.4	10	23.8	13	30.9
Antibody response; tonsils intact	201	5	2.5	9	4.5	20	9.9	39	19.4	48	23.8	80	39.9
Antibody response; tonsils absent	99	2	2.0	4	4.0	11	11.0	20	20.2	22	22.2	40	40.5
Scarlet fever	27	0	0.0	0	0.0	3	11.1	4	14.8	6	22.2	14	51.9
Cervical adenitis													
Absent	62	2	3.2	7	11.3	11	17.7	17	27.4	12	19.3	13	21.0
1 plus	132	3	2.2	7	5.3	14	10.6	24	18.2	29	21.9	55	41.6
2 and 3 plus	148	2	1.3	2	1.3	13	8.8	27	18.2	39	26.4	65	43.9
Pharyngeal exudate													
Absent	126	4	3.2	8	6.3	20	15.9	26	20.6	30	23.8	38	30.2
1 plus	60	0	0.0	3	5.0	6	10.0	17	28.3	19	31.6	15	25.0
2 plus	81	1	1.2	2	2.5	9	11.1	10	12.3	10	12.3	49	60.5
3 plus	75	2	2.7	3	4.0	3	4.0	15	20.0	21	28.0	31	41.3

TABLE 2.—*Duration of Fever in Hemolytic Streptococcic Sore Throat*

	No. of Cases	Afebrile		1		2		3		4		5		6 and Over	
		No.	%	No.	%	No.	%	No.	%	No.,	%	No.	%	No.	%
Antibody response	300	6	2.0	55	18.3	79	26.3	73	24.3	44	14.7	14	4.6	29	9.7
No antibody response	42	0	0.0	0	0.0	12	28.6	14	33.3	3	7.1	3	7.1	1	2.4
Antibody response															
Tonsils intact	201	5	2.5	40	19.9	49	24.4	52	25.8	30	14.9	5	2.5	20	9.9
Tonsils absent	99	1	1.0	15	15.1	30	30.3	21	21.2	14	14.1	9	9.1	9	9.1
Scarlet fever	27	0	0.0	2	7.4	1	3.7	4	14.8	7	25.9	6	22.2	7	25.9
Cervical adenitis															
Absent	62	2	3.2	18	29.0	16	25.8	11	17.7	6	9.7	5	8.1	4	6.5
1 plus	132	2	1.5	26	19.7	34	25.7	33	25.0	21	15.0	7	5.3	9	6.8
2 or 3 plus	148	2	1.3	20	13.5	41	27.7	43	29.1	20	13.5	5	3.4	17	11.4
Pharyngeal exudate															
Absent	126	3	2.4	32	25.4	31	24.6	24	19.0	24	19.0	4	3.2	8	6.3
1 plus	60	0	0.0	11	18.3	16	26.6	20	33.3	6	10.0	3	5.0	4	6.7
2 plus	81	1	1.2	12	14.8	19	23.5	25	30.9	10	12.3	5	6.2	9	11.1
3 plus	75	2	2.7	8	10.7	25	33.3	19	25.3	7	9.3	5	6.7	9	12.0
Serologic type															
Type 3	33	0	0.0	7	21.2	7	21.2	7	21.2	7	21.2	2	6.1	3	9.1
Type 17	28	0	0.0	4	14.3	2	7.1	3	10.7	11	39.3	1	3.6	7	25.0
Type 19	42	0	0.0	6	14.3	9	21.4	12	28.6	4	9.5	5	11.9	6	14.3
Type 30	20	0	0.0	2	10.0	8	40.0	4	20.0	2	10.0	2	10.0	2	10.0
Type 36	58	2	3.4	12	20.7	22	37.9	14	24.2	4	6.9	2	3.4	2	3.4
Type 46	15	0	0.0	3	20.0	6	40.0	2	13.3	2	13.3	0	0.0	2	13.3
Therapy															
Sulfadiazine	37	1	2.7	5	13.5	8	21.6	7	18.9	5	13.5	2	5.4	9	24.3
Sulfadiazine and penicillin	28	0	0.0	1	3.6	2	7.1	4	14.3	10	35.7	6	21.4	5	17.7
Penicillin, short course	20	0	0.0	1	5.0	5	25.0	8	40.0	1	5.0	0	0.0	5	25.0
Penicillin, long course	13	0	0.0	1	7.7	5	38.5	3	23.0	2	15.4	1	7.7	1	7.7
Salicylates	27	1	3.7	4	14.8	4	14.8	13	48.2	4	14.8	1	3.7	0	0.0

ture fell to normal for one or more days, later to rise again. In others the temperature remained elevated for various reasons. It is, however, obvious that the exhibition of sulfonamide drugs or penicillin cannot be expected to terminate rapidly the febrile phase of acute hemolytic streptococcic sore throat.

The mean duration of fever was four days in sulfonamide-treated patients infected by streptococci moderately resistant to sulfonamide drugs and three and a half days in those in whom the infectious agent was highly susceptible to the antibacterial action of these chemicals. It is clear that the failure of sulfonamide therapy to shorten the febrile course of the disease was not the result of inclusion in the study group of numerous examples of infection by resistant organisms.

Only 1 of the group of 27 patients who received large doses of salicylates throughout their stay in the hospital was febrile for more than four days. This is a statistically significant result if the comparison is made with the first three treatment groups, but not if made with the mean result for all cases.

Among 17 cases in which fever was demonstrated for five days but not longer, there were 7 instances of scarlet fever, 5 examples of an unusually severe local lesion in the throat, 1 case in which a nonsuppurative disorder with arthritis supervened on the second day of illness [9] and 3 cases in which no explanation of the prolonged febrile course was discovered.

Fever persisted for six or more days in 30 cases. This occurred in 5 because of relapse following the premature withdrawal of the use of penicillin and in 2 because of reinfection by a new type of hemolytic streptococcus early in the course of the disease. Severe local suppuration in the throat, either incipient or established peritonsillar abscess or severe cervical adenitis was discovered in 7. The syndrome of uncomplicated scarlet fever was present in 3 cases, and in 3 others suppurative sinusitis was diagnosed. The cause of the prolonged fever was not determined in 4 cases. It was believed in 5 others that a nonsuppurative complication had become established early in the course of the acute illness. These cases will be described elsewhere.[2b]

Duration of Abnormal Signs.—The duration of abnormal signs, including the presence of exudate, edema and redness involving the pharyngeal tissues and tender adenitis of the anterior cervical region, was recorded and the data summarized in table 3. The throat and neck had returned to normal within one to two days in 23.6 per cent and within three to four days in 68.2 per cent of proved cases.

The presence of an antibody response, tonsils or cutaneous rash did not alter the duration of abnormal signs. They did persist for a

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9. The administration of salicylates was followed by a prompt return of the temperature to normal.

TABLE 3.—*Duration of Abnormal Physical Signs in Hemolytic Streptococcic Sore Throat*

| | No. of Cases | Duration of Abnormal Signs, Days | | | | | | | | | |
| | | None | | 1 to 2 | | 3 to 4 | | 5 to 6 | | 7 or More | |
		No.	%	No.	%	No.	%	No.	%	No.	%
Antibody response..........	300	13	4.3	58	19.3	134	44.6	57	19.0	38	12.7
No antibody response..........	42	3	7.1	5	11.9	21	50.0	8	10.0	5	11.9
Antibody response; tonsils intact..........	201	9	4.5	27	13.4	85	42.3	52	25.8	28	13.9
Antibody response; tonsils absent..........	99	4	4.0	31	31.3	49	49.5	5	5.0	10	10.1
Scarlet fever..........	27	1	3.7	5	18.5	13	48.2	4	14.8	4	14.8
Cervical adenitis											
Absent..........	62	10	16.1	21	33.9	22	35.5	5	8.1	4	6.5
1 plus..........	132	4	3.0	34	25.7	62	47.0	22	16.7	10	7.6
2 or 3 plus..........	148	2	1.3	8	5.4	71	48.0	38	25.6	29	19.6
Pharyngeal exudate											
Absent..........	126	14	11.1	42	33.3	51	40.5	10	7.9	9	7.1
1 plus..........	60	1	1.7	14	23.4	33	55.0	9	15.0	3	5.0
2 plus..........	81	1	1.2	3	3.7	43	53.1	17	21.0	17	21.0
3 plus..........	75	0	0.0	4	5.3	28	37.3	29	38.7	14	18.7
Therapy											
Sulfadiazine..........	37	0	0.0	5	13.5	12	32.4	10	27.0	10	27.0
Sulfadiazine and penicillin..........	28	0	0.0	2	7.1	8	28.6	6	21.4	12	42.9
Penicillin, short course..........	20	1	5.0	2	10.0	5	25.0	7	35.0	5	25.0
Penicillin, long course..........	13	0	0.0	0	0.0	4	25.0	5	38.5	4	30.8
Salicylates..........	27	1	3.7	5	18.5	14	51.9	5	18.5	2	7.4

significantly longer time in cases in which decided cervical adenitis was noted than in those in which it was not. Similarly, there was a direct correlation between the amount of exudate and the persistence of abnormalities. If exudate (2 or 3 plus) was described initially, the throat required more than five days in almost 50 per cent and seven or more days in approximately 20 per cent of cases to return to normal.

Infection by none of the six serologic types resulted in a disease process associated with a significantly long or short duration of abnormalities in the throat and neck. The data on which this statement is based have, therefore, been omitted from the table.

The administration of neither sulfadiazine, penicillin nor a combination of the two shortened the duration of abnormal physical signs. This result was not affected by the degree of resistance of the infectious agent to sulfonamide drugs. The patients treated with these two chemicals did, in fact, have pathologic signs for a significantly longer period than did the group as a whole. The explanation of this fact is probably similar to that offered in regard to the effect of chemotherapy on the duration of fever. It is clear, however, that the use of these drugs in cases of severe conditions is not associated with an immediate return of the diseased tissues to a normal state.

Suppurative Complications.—A variety of suppurative complications followed acute hemolytic streptococcic sore throat during this study. Their nature will be summarized.

Otitis media developed in 5 cases. On three occasions, it was present on or shortly after the patient's admission to the hospital and extremely near the onset of the acute illness. The type of Streptococcus isolated from the throat and ear was the same in these cases. Involvement of the ear occurred on the tenth and nineteenth day of illness in 2 other cases. In both, a strain of hemolytic streptococcus of group G was isolated from the purulent discharge obtained from the ear. Each of these 5 patients received sulfonamide therapy, the response being excellent.

A peritonsillar abscess ruptured in 2 cases before and in 2 after admission to the hospital. The administration of adequate amounts of sulfadiazine failed to bring about resolution of the process in the latter cases. There can be little doubt, however, that the use of this chemical, penicillin or the two agents in combination did prevent the development of tonsillar abscess on a number of occasions.

There were 6 patients in whom suppurative sinusitis appeared to be the cause of prolonged or recurrent fever and disability of unusual duration. An erythrocyte sedimentation rate of more than 25 mm. per hour was discovered three weeks after the onset of the initial illness in 6 additional cases. No definite clinical evidence of a disease process was present in any of these men, but cultures of material from the nose

which were strongly positive for organisms at the time of follow-up examination suggested that the continuing reaction of the tissues was the result of infection of the paranasal sinuses. A similar process was doubtless present in many other cases but cleared spontaneously or failed to increase or prolong disability and was therefore not diagnosed. Certain aspects of this problem were studied in this same group of patients by Hamburger, Green and Hamburger.[10]

The erythrocyte sedimentation rate also remained elevated for three or more weeks in 9 additional patients in whom the initial suppurative process in the throat had been unusually severe. No evidence of disability or continuing illness was demonstrable in any of these patients at the follow-up examination.

The prompt recovery in 18 cases not previously mentioned was hampered by the occurrence of a clinical relapse following the discontinuance of therapy consisting of penicillin alone or followed by sulfadiazine. This subject has been considered fully elsewhere.[6]

The convalescence of a small group of patients was complicated by reinfection with a new type of group A hemolytic streptococcus associated with the development of frank clinical signs of disease. In others a similar event occurred, but only alterations in the results of laboratory tests indicated that a new infection had supervened. It has been noted previously that reinfection may be related to the development of nonsuppurative complications.[2a] It is more appropriate, therefore, to consider these cases in the paper devoted to the latter disorders.

CLINICOPATHOLOGIC OBSERVATIONS

Erythrocyte Sedimentation Rate.—The measurement of the erythrocyte sedimentation rate is an accepted method for the estimation of the severity and duration of the reaction of the tissue to infection by a variety of micro-organisms. The rates were determined initially in 342 and three weeks later in 299 of these cases of hemolytic streptococcic sore throat. The information obtained has been exhaustively analyzed and the effect of various clinical manifestations of the disease evaluated.

The values obtained during the initial phase of the disease have been described previously.[1] It was noted that the rate was greater than 20 mm. per hour in 70.8 per cent, greater than 30 mm. per hour in 50.1 per cent, greater than 40 mm. per hour in 32.7 per cent and greater than 50 mm. per hour in 19.4 per cent of the proved cases. No correlation existed between the presence of an antibody response, tonsils or a cutaneous rash and the initial erythrocyte sedimentation rate.

10. Hamburger, M.; Green, M. J., and Hamburger, V. G.: The Problem of the Dangerous Carrier of Hemolytic Streptococci: I. Number of Hemolytic Streptococci Expelled by Carriers with Positive and Negative Nose Cultures, J. Infect. Dis. **77**:68, 1945.

The results of other analyses made since that time are presented in table 4. The frequency of occurrence of rates greater than 40 mm. per hour on the initial examination and 30 mm. per hour on the follow-up examination have been used as indexes for study. If any correlation

TABLE 4.—*Initial and Follow-up Erythrocyte Sedimentation Rates in Hemolytic Streptococcic Sore Throat* ·

	Initial Erythrocyte Sedimentation Rate			Erythrocyte Sedimentation Rate on the 19th to 25th Day		
	No. Studied	No. with Rate Greater Than 40 Mm./Hr.	Per Cent with Rate Greater Than 40 Mm./Hr.	No. Studied	No. with Rate Greater Than 30 Mm./Hr.	Per Cent with Rate Greater Than 30 Mm./Hr.
Antibody response...................	294	96	32.7	262	51	19.4
No antibody response...............	41	8	19.5	37	3	8.1
Antibody response; tonsils intact....	198	66	33.3	174	33	18.9
Antibody response; tonsils absent...	96	30	31.2	88	18	20.4
Scarlet fever........................	26	7	26.9	26	11	42.3
Cervical adenitis						
Absent.........................	63	15	23.8	56	5	8.9
1 plus.........................	128	40	31.2	116	21	18.1
2 or 3 plus...................	144	49	34.1	127	28	22.0
Pharyngeal exudate						
Absent.........................	123	38	30.9	110	18	16.4
1 plus.........................	59	21	35.6	50	12	24.0
2 plus.........................	81	24	29.6 ,	70	12	17.1
3 plus.........................	72	21	29.2	69	12	17.8
Maximum temperature						
Afebrile to 99.9 F.............	23	4	17.4	21	1	4.8
100.0 to 100.9 F..............	38	10	26.3	35	3	8.5
101.0 to 101.9 F..............	65	12	18.4	57	6	10.6
102.0 to 102.9 F..............	77	32	41.6	69	15	21.7
103.0 F. and over.............	132	46	35.1	117	29	24.7
Duration of fever						
1 day or less.................	70	14	20.0	60	7	11.6
2 days........................	88	22	27.3	78	9	11.5
3 days........................	86	25	29.1	78	14	17.9
4 days........................	46	24	52.1	40	8	20.0
5 days........................	16	5	31.2	16	6	37.5
6 days or more................	29	12	41.3	27	10	37.0
Serologic type						
Type 3........................	33	10	30.4	31	6	19.2
Type 17.......................	26	14	53.8	26	5	19.2
Type 19.......................	41	19	46.3	37	5	13.5
Type 30.......................	20	9	45.0	20	8	40.0
Type 36.......................	56	13	23.2	48	10	20.7
Type 46.......................	15	7	46.7	14	4	28.6
Therapy						
Sulfadiazine..................	34	19	55.9	33	6	18.2
Sulfadiazine and penicillin...	28	11	39.2	28	6	21.4
Penicillin, short course......	19	3	15.8	18	7	38.9
Penicillin, long course.......	13	4	30.8	13	2	15.4
Salicylates...................	27	7	25.9	24	3	12.5

appeared to exist in any category, further examination was made of the relationship of the occurrence of slower rates to the clinical manifestation in question. The limitations of space forbid the presentation of all these data in tabular form.

There was no relationship between the severity of cervical lymphadenitis, the amount of exudate in the throat, the maximum temperature,

the duration of fever or the serologic type of Streptococcus and the occurrence of extremely rapid initial erythrocyte sedimentation rates. None of the differences discernible in the table are greater than those to be expected on the basis of chance.

The erythrocyte sedimentation rate was greater than 20 mm. per hour in 30.8 per cent and greater than 30 mm. per hour in 19.4 per cent of proved cases nineteen to twenty-five days after the onset of the illness. The data presented in the table suggest that the rates at this time were more prolonged, with increasing severity of cervical adenitis, greater height of maximum temperature, more prolonged febrile course and the presence of a cutaneous rash or of an antibody response. Although these associated variations would not be unexpected, none deviates sufficiently from the mean to be of definite significance. It is possible that the stated trends are real and could be confirmed by the study of a larger group of cases.

TABLE 5.—*Relationship Between Initial and Follow-up Erythrocyte Sedimentation Rates in Hemolytic Streptococcic Sore Throat*

Initial Erythrocyte Sedimentation Rate	No. Done	Erythrocyte Sedimentation Rate on 18th to 25th Day									
		Less than 9		10 to 19		20 to 29		30 to 39		40 and Over	
		No.	%	No.	%	No.	%	No.	%	No.	%
Less than 9	29	26	89.8	1	3.4	1	3.4	0	0.0	1	3.4
10 to 19	61	48	78.6	8	13.1	4	6.5	0	0.0	1	1.6
20 to 29	62	35	56.5	14	22.6	5	8.1	4	6.4	4	6.4
30 to 39	51	24	47.0	9	17.6	7	13.7	4	7.8	7	13.7
40 to 49	38	13	34.2	10	26.2	5	13.1	6	15.8	4	10.5
50 and over	53	8	15.1	13	24.5	11	20.7	8	15.1	13	24.5

It is obvious from an inspection of the table that the erythrocyte sedimentation rate at the end of three weeks was not influenced by the amount of exudate in the throat, the presence of tonsils, the serologic type of infecting Streptococcus, the utilization of antibacterial chemotherapy or the administration of salicylates.

The relationship of the initial erythrocyte sedimentation rate to that obtained approximately three weeks later is indicated by the data presented in table 5. There was a direct correlation between the two values. The follow-up rate was normal (less than 20 mm. per hour) in only 48.5 per cent of cases in which the initial rate was 40 mm. per hour or more. Conversely, if the initial rate was within normal limits, the follow-up rate was also within normal limits in 92.0 per cent of cases. It is important to point out that the follow-up rates were more rapid than the initial in a considerable number of cases. Some of these patients suffered from nonsuppurative complications and will be described elsewhere.

Total Leukocyte Count.—The total leukocyte count was determined on approximately the second day of illness in 342 cases. The data are

presented in table 6.   The count was greater than 9,000 per cubic millimeter in 76.9 per cent, greater than 13,000 in 49.1 per cent and greater than 16,000 in 26.7 per cent of proved cases.   The presence of an antibody response, tonsils or cutaneous rash did not significantly affect these values.   If the counts below 16,000 cells per cubic millimeter are considered, certain trends are observed which are not of definite statistical significance.   Thus, the total count is higher with increasing severity

TABLE 6.—*The Initial Total Leukocyte Count in Hemolytic Streptococcic Sore Throat*

	No. of Cases	Initial Leukocyte Count in Thousands							
		Less than 9,000		10,000 to 12,900		13,000 to 15,900		16,000 and Up	
		No.	%	No.	%	No.	%	No.	%
Antibody response.....................	299	69	23.1	83	27.8	67	22.4	80	26.7
No antibody response.................	42	14	33.3	11	26.2	12	28.6	5	11.9
Antibody response; tonsils intact.....	201	43	21.4	53	26.4	49	24.4	56	27.8
Antibody response; tonsils absent.....	98	26	26.5	30	30.6	18	18.7	24	24.5
Scarlet fever..........................	27	5	18.5	6	22.2	6	22.2	10	37.0
Cervical adenitis									
Absent............................	62	22	35.5	22	35.5	8	12.9	10	16.1
1 plus............................	131	33	25.2	40	30.6	35	26.7	23	17.5
2 or 3 plus........................	148	29	19.6	32	21.6	36	24.4	51	34.4
Pharyngeal exudate									
Absent............................	126	42	33.3	39	30.9	25	19.8	10	15.9
1 plus............................	59	10	16.9	19	32.2	14	23.7	16	27.1
2 plus............................	81	19	23.5	17	21.0	22	27.2	23	28.4
3 plus............................	75	13	17.3	19	25.3	18	24.0	25	33.3
Maximum temperature									
Afebrile to 99.9 F..................	23	8	34.8	9	39.1	5	21.7	1	4.4
100.0 to 100.9 F....................	38	16	42.1	10	26.3	9	23.7	3	7.9
101.0 to 101.9 F....................	68	21	30.9	18	26.5	10	14.7	19	27.9
102.0 to 102.9 F....................	80	13	16.2	26	32.5	24	30.0	17	21.3
103.0 F. and up....................	132	26	19.7	31	23.5	31	23.5	44	33.3
Duration of fever									
Afebrile to 1 day..................	70	26	37.2	24	34.3	16	22.9	4	5.7
2 days............................	91	32	35.1	26	28.6	20	22.0	13	14.3
3 days............................	86	12	13.9	22	25.6	23	26.7	29	33.8
4 days............................	47	5	10.6	14	29.8	11	23.4	17	36.2
5 days............................	17	4	23.5	2	11.7	5	29.4	6	35.3
6 days and up.....................	30	5	16.7	6	20.0	4	13.3	15	50.0
Therapy									
Sulfadiazine......................	37	11	29.7	10	27.0	5	13.5	11	29.7
Sulfadiazine and penicillin........	28	5	17.8	5	17.8	1	3.6	17	60.7
Penicillin, short course............	20	4	20.0	3	15.0	5	25.0	8	40.0
Penicillin, long course.............	13	2	15.4	2	15.4	4	30.8	5	38.4
Salicylates........................	27	2	7.4	9	33.3	9	33.3	7	25.9

of adenitis, amount of exudate, height of maximum temperature and duration of fever.   When the counts above 16,000 per cubic millimeter are analyzed, the trends just mentioned are emphasized and become significant.   If the maximum temperature was greater than 101 F. or if fever was to persist for more than three days, the number of extremely high counts was strikingly increased, as it was in patients with severe cervical adenitis or large amounts of exudate in the throat.   No correlation between the serologic type of infecting Streptococcus and the total initial leukocyte count was discovered, and the data have been omitted from the table.

The analysis of the leukocyte count, obtained about nine days after the onset of the acute illness in 306 cases, was not particularly illuminating, since at this time there had been only a moderate return of the values to normal and all the relationships previously noted were maintained at slightly lower levels. That this should have been the case is remarkable when the data presented in table 7 are evaluated. In it the initial total leukocyte count is compared with the count obtained at about nine days in the same patients. In many cases the count, if elevated, returned toward normal, but on others, making up more than one third of the whole group, there was a moderate to pronounced

TABLE 7.—*Relationship Between Initial Leukocyte Counts and Those Obtained on the Eighth to Tenth Day of Hemolytic Streptococcic Sore Throat*

		Leukocyte Count on 8th to 10th Day							
		Less than 9,000		10,000 to 12,900		13,000 to 15,900		16,000 and Up	
Initial Leukocyte Count	No. Done	No.	%	No.	%	No.	%	No.	%
9,000 or less..........................	74	37	50.0	17	23.0	9	12.2	11	14.8
10,000 to 12,900......................	111	28	25.2	31	27.9	33	29.7	19	17.1
13,000 to 15,900......................	64	9	14.0	21	32.8	19	29.7	15	23.4
16,000 and up........................	56	4	7.1	12	21.4	10	17.9	30	53.6

increase in the total number of leukocytes. An explanation for this phenomenon occurring in a large number of patients, most of whom were recovering rapidly from their illness, is not immediately forthcoming.

Neither any of the antibacterial therapeutic regimens nor the administration of sodium salicylate significantly reduced the frequency of occurrence of elevated leukocyte counts at the second examination.

BACTERIOLOGIC OBSERVATIONS

The results obtained on the initial cultures of material from the nose and throat in this group of cases of hemolytic streptococcic sore throat, including the distribution of the isolated strains among the various Lancefield types, have been described.[11] The natural history of the carrier state of group A hemolytic streptococci and the effect on it of chemotherapy will be recounted at this time. The essential data are enumerated in table 8. Approximately 75 per cent of the patients with proved infection remained pharyngeal carriers of hemolytic streptococci on the eighth to tenth day of the illness. The incidence of nasal carriers had decreased from about 65 to 28 per cent at this time. These rates at this stage of the disease were similar whether an antibody response, tonsils or a cutaneous rash had or had not been present.

11. Rantz, L. A.; Rantz, H. H.; Boisvert, P. J., and Spink, W. W.: Streptococcic and Nonstreptococcic Disease of the Respiratory Tract: Epidemiologic Observations, Arch. Int. Med. **77**:121 (Feb.) 1946.

TABLE 8.—*Course of the Carrier State in Hemolytic Streptococcic Sore Throat*

	Initial Cultures, Nose			Cultures at 8 to 10 Days						Cultures at 19 to 25 Days					
				Throat			Nose			Throat			Nose		
	No.	No. Positive	% Positive	No.	No. Positive	% Positive	No.	No. Positive	% Positive	No.	No. Positive	% Positive	No.	No. Positive	% Positive
Antibody response	230	151	65.7	267	200	75.0	240	68	28.3	222	146	65.8	227	52	22.9
No antibody response	39	19	48.7	36	27	75.0	32	14	43.7	36	16	44.4	35	4	11.4
Antibody response															
Tonsils intact	193	122	63.2	177	135	76.3	160	44	27.5	150	108	72.0	150	33	22.0
Tonsils absent	96	68	70.9	90	65	72.2	80	24	30.0	72	33	52.8	77	19	24.7
Scarlet fever	25	19	76.0	15	12	80.0	8	3	37.5	9	5	55.6	7	4	57.1
Serologic type															
Type 3	33	19	57.5	30	11	36.7	32	5	15.6	29	9	31.0	30	2	6.7
Type 17	26	18	69.3	27	22	81.5	23	11	47.8	19	13	68.4	20	4	20.0
Type 19	40	24	60.0	39	33	84.6	32	10	31.2	34	30	88.3	35	12	34.3
Type 30	20	14	70.0	18	16	88.9	16	10	62.5	8	8	100.0	12	5	41.7
Type 36	53	39	73.6	46	35	76.1	39	12	30.7	47	29	61.7	48	10	20.8
Type 46	15	11	73.4	15	11	73.4	14	4	28.5	11	7	63.7	12	2	16.6
Therapy															
None	209	122	58.5	189	152	80.1	171	58	33.0	161	97	60.2	169	30	17.7
Sulfadiazine	34	27	79.5	32	22	68.8	28	7	25.0	28	20	71.4	29	7	24.1
Sulfadiazine and penicillin	27	19	70.4	28	20	71.4	23	5	21.7	21	14	66.6	25	6	24.0
Penicillin, short course	19	14	73.7	20	20	100.0	17	6	35.3	17	13	76.5	17	7	41.1
Penicillin, long course	12	7	58.4	12	4	33.3	11	2	18.2	10	4	40.0	11	2	18.2
Salicylates	27	20	74.0	22	14	63.6	22	4	18.2	21	15	71.5	20	4	20.0
Sulfadiazine or sulfadiazine after penicillin															
Sulfonamide-sensitive organisms	23	18	78.3	22	16	72.7	19	4	21.0	19	15	78.9	20	6	30.0
Sulfonamide-resistant organisms	32	24	75.0	32	23	71.9	22	7	31.8	26	19	73.1	28	7	25.0

Only a slight diminution in the number of pharyngeal and nasal car-riers occurred during the following two weeks. Hemolytic streptococci were recovered from the throat less frequently at the end of three weeks, if the tonsils had been removed. The absence of these organs did not affect the rate of nasal carriers.

The occurrence of group A carriers was evaluated in relationship to the serologic types of the etiologic agent, and the results are presented in table 8 because significant information was obtained. Pharyngeal car-riers were less frequently discovered at eight to ten and at nineteen to twenty-five days when the etiologic agent was a strain of type 3.

The incidence of cultures of material from the nose yielding pathogens also varied with the serologic type of the infecting organism. Differences in the rate of nasal carriers, which had begun to manifest themselves at the end of the first week, were definite two weeks later in that there were less patients with infection of type 3 and more with infection of type 19 still harboring hemolytic streptococci in the nose than were members of the whole group, or those infected by the other four types. These differences are not the result of the use of any antibacterial chemical and are statistically significant.

The effect of antibacterial chemotherapy on the state of the carriers of group A hemolytic streptococci has been summarized previously.[12] The data on which this report was based are presented in the last eight lines of table 8. Only brief comment on this matter is necessary, since administration of neither sulfadiazine nor penicillin, alone or in combination, resulted in a significant diminution in the incidence of pharyngeal or nasal carriers of group A streptococci. The persistence of hemolytic streptococci in the upper air passages of all sulfonamide-treated patients was analyzed with reference to the sensitivity of the etiologic agent to sulfonamide drugs. The frequency of occurrence of pharyngeal and nasal carriers at the various intervals in the two groups was similar. It is unlikely, therefore, that the failure of sulfadiazine to eliminate hemolytic streptococci from the nose and throat in these cases was the result of the presence of organisms moderately resistant to sulfonamide drugs as the cause of many of the infections. It should be noted that these organisms were permanently eradicated from the naso-pharynges of at least 7 men who received the "long course" of penicillin.

COMMENT

Only a brief discussion of this purely factual description of the course of acute hemolytic streptococcic sore throat in young men is necessary. The essential data are presented in tables and brief comments made with special reference to the results of statistical analyses that had been car-

12. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Chemotherapy and the Hemolytic Streptococcus Carrier State, Bull. U. S. Army M. Dept. 5:662, 1946. Rantz and associates.[1]

ried out. A detailed narrative description of all the observations was impossible because of the limitations of space.

The disease had a variable course, as was to be expected. The temperature rose to 102 F. or more in 63.3 per cent and remained elevated for not more than three days in 71.0 per cent of all cases in which infection was proved by the presence of an antibody response. All physical signs had disappeared from the throat and neck within four days in 68.2 per cent of the same group of cases. A prolonged febrile course was usually associated with the presence of a cutaneous rash, of an unusually severe suppurative process in the throat or a suppurative complication. In a few patients, the early supervention of a nonsuppurative complication prolonged the period of disability.

The severity and frequency of occurrence of the clinical manifestations of the disease were extensively correlated with one another and with the laboratory observations. It was anticipated that the magnitude of the involvement of the pharyngeal tissues, as estimated by palpation of the neck and inspection of the pharynx, would be closely related to the degree and duration of fever, but this was not the case. Significantly lower temperatures were noted in patients without tender cervical adenitis, but the height of temperature did not reflect the amount of exudate in the throat. The febrile phase of the illness was of greater length when a cutaneous rash was present but was not affected by the magnitude of other physical abnormalities. The persistence of abnormal physical signs was directly correlated with the extent of the initial lesion in the throat.

The erythrocyte sedimentation rate was usually more rapid than normal on the second or third day of acute hemolytic streptococcic sore throat. The magnitude of this abnormality was not well correlated with the usual clinical manifestations used to measure the severity of the infectious process. Neither the height of the maximum temperature, the duration of fever, the degree of estimated abnormality of the pharyngeal tissues nor a cutaneous rash could be shown to be significantly associated with the initial erythrocyte sedimentation rate. Later, when this laboratory procedure was carried out during convalescence, there was a relationship between the severity of the previously observed illness and the erythrocyte sedimentation rate which was more nearly significant and may well measure an actual correlation.

The number of total leukocytes varied with the severity of the demonstrable suppurative process in the throat but most strikingly with the height of maximum temperature and duration of the febrile illness.

The lack of statistical correlation between the frequency of occurrence, severity and degree of abnormality of the various clinical signs and laboratory procedures strongly suggests that these manifestations of the infectious process do not have a common pathogenesis. Thus the product or function of the hemolytic streptococcus that stimulates and

maintains fever does not appear to be the same as that which incites the formation of the lesion in the pharyngeal tissues. Leukocytosis was most actively provoked by the fever-producing agent. No definite relationship between either factor and the erythrocyte sedimentation rate was discovered, suggesting that a third pathologic mechanism was operative.

It is not the purpose of this paper to elucidate in detail the pathogenesis of the various manifestations of hemolytic streptococcic sore throat. The information just presented suggests that the infectious process is complex.

Certain of the manifestations of the disease must be the result of the direct toxic action of the metabolic products of the multiplying organism acting locally or systemically. Others may well result from an altered or "allergic" reaction of the tissues of the host to these products as the result of previous infection by the hemolytic streptococcus. Evidence has been presented which indicates that the cutaneous rash may result from the action of such a mechanism.[13] Another group of investigators has suggested that the observed differences between the natural history of hemolytic streptococcic respiratory disease in infants and in older children and adults are the consequence of a reaction of the tissue altered in the latter by earlier exposure to the organism.[14]

A variety of therapeutic regimens, involving the administration of varying amounts of penicillin, alone or in combination with sulfadiazine or the latter drug alone, were instituted. The number of cases in each treatment group is not large, and no true controls are available, since the most severely ill patients usually received antibacterial therapy. The evidence presented herein demonstrates that none of the several regimens sharply terminated the febrile illness, induced a dramatic resolution of the suppurative lesion in the throat or led to an unusually rapid return to normal of the various laboratory tests. It is possible that suppurative complications were prevented in certain cases, but this may only be inferred. This analysis, which indicates the relative inefficacy of the chemotherapy of hemolytic streptococcic sore throat, is in accord with one made previously using part of these data.[6]

The natural history of sore throat caused by each of six serologic types of group A hemolytic streptococci was analyzed and compared. Biologic differences existed between strains of the various types. In spite of this fact, the signs and symptoms of the initial phase of the infection, its course and the degree of abnormality of the various

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13. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: The Dick Test in Military Personnel with Special Reference to the Pathogenesis of the Skin Reaction, New England J. Med. **39**:235, 1946.

14. Bearg, P. A.; Boisvert, P. J.; Darrow, D. C.; Powers, G. F., and Trask, J. D.: "Streptococcosis" and "Streptococcic Fever," Am. J. Dis. Child. **62**:431 (Aug.) 1941.

laboratory tests were similar, regardless of the type of etiologic agent. Infection by four of the types (3, 17, 19, and 30) was associated with a cutaneous rash in certain persons, and the febrile course of the illness was in these circumstances more prolonged.

The information obtained during this study permits a description of the first three weeks of the carrier state of group A hemolytic streptococci in young adults. The organisms were isolated from the pharynxes of 99 per cent and from the noses of 65 per cent of these patients at the onset of the illness. One week later 75 per cent were proved to be pharyngeal and 28 per cent nasal carriers. Only an extremely slight diminution in the number of carriers occurred during a subsequent two weeks' period of observation. A persistent pharyngeal carrier state was established less often in persons in whom the tonsils had been removed. The absence of these organs had no effect on the occurrence of nasal carriers. Strains of type 3 persisted in the throat and nose for a shorter and strains of type 19 for a longer period than did those of other types.

Persons harboring hemolytic streptococci in the upper air passages, particularly the nose,[10] often transmit these organisms to susceptible human beings. It is worth while, therefore, to emphasize the fact that a large number of these infected men became persistent pharyngeal and nasal carriers and that none of the antibacterial therapeutic regimens was effective in the elimination of the organism from the throat and nose.

SUMMARY

1. The natural history of the acute suppurative phase of group A hemolytic streptococcic sore throat in young adults has been described.

2. The degree and duration of fever and the initial erythrocyte sedimentation rate were poorly correlated with the degree of physical abnormality of the throat and neck.

3. A more prolonged febrile illness occurred if a cutaneous rash was present.

4. The initial leukocyte count varied with the severity of the acute disease.

5. A rash occurred only when the infecting Streptococcus was of type 3, 17, 19 or 30. The disease caused by six serologic types was otherwise similar.

6. The first three postinfectious weeks of the group A carrier state have been described.

7. Several therapeutic regimens, involving the administration of sulfadiazine and penicillin, alone and in combination, were utilized. None effectively terminated the disease or consistently eradicated the hemolytic streptococcus from the nose and throat.

BRONCHIOGENIC ADENOMA

Benign Tumor of the Bronchus

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WHAT IS known today as polypoid adenoma of the bronchus was observed and recorded by Laennec in his treatise on ausculation. Laennec[1] wrote:

It is rare for polypoid excrescences to develop on the mucous membrane of the bronchi; only three examples are known to me. It seems that these excrescences are of the type of vascular polyps of the nose, ears and uterine cervix, that is to say, they are formed by tissue analogous to the mucous membrane containing small serous cysts.

The literature contains a reference to Mueller,[2] who accidentally found an instance of the condition at autopsy but ignored completely Laennec's observation. After the appearance of Mueller's article the disease was identified by pathologists, and after the introduction of the bronchoscope it was recognized in the clinic. Chiefly American and British physicians are responsible for the interest evinced in the disease. Patterson[3] and Yankauer[4] were among the first to report cases. Patterson found 26 cases in the available literature, in 10 of which the disease was disclosed at necropsy; in the remaining 16 it had been diagnosed bronchoscopically. Kramer[5] outlined clinical features, bronchoscopic treatment and the use of radon seeds. Kramer's studies were further developed by Wessler and Rabin,[6] but particularly important were the extensive studies by Chevalier Jackson.[7]

1. Laennec, R.: Traité de l'auscultation mèdiate et des maladies des poumons et du cœur, ed. 3, Paris, J. S. Chaudé, 1831, vol. 1, p. 250.

2. Mueller, H.: Zur Entstehungsgeschichte der Bronchialerweiterungen, Halle, A. Busch, 1882.

3. Patterson, E. J.: Benign Bronchial Neoplasms, Arch. Otolaryng. **12**:739 (Dec.) 1930.

4. Yankauer, S.: Laryngoscope **39**:649, 1929.

5. Kramer, R.: Ann. Otol., Rhin. & Laryng. **39**:689, 1930.

6. Wessler, H., and Rabin, C.: Am. J. M. Sc. **183**:164, 1932.

7. Jackson, C., and Jackson, C. L.: Benign Tumors of Trachea and Bronchi, with Especial Reference to Tumor-Like Formations of Inflammatory Origin, J. A. M. A. **99**:1747 (Nov. 19) 1932.

Morlock and Pinchin,[8] Foster-Carter,[9] Kramer and Som [10] and Lowry and Rigler [11] estimated that adenoma of the bronchus is the commonest benign bronchial tumor and that it occurs in about 6 per cent of all bronchial neoplasms. Of 243 cases of bronchiogenic tumors studied bronchoscopically in fifteen years, Clerf and Bucher [12] observed adenomas in 35, or 12 per cent. It is significant that in spite of their accessibility in barely one half of the cases was the condition diagnosed during life.

<div align="center">PATHOLOGY ·</div>

The adenoma starts in the mucosa or submucosa of a large bronchus, whose diameter is at least 10 mm. The notion that it always spreads in the direction of the bronchial lumen, leaving the parenchyma of the lung intact, has been contradicted by recent observations. It appeared that in the majority of cases the tumor advances in two directions—toward the bronchial lumen and toward the parenchyma of the lung. In its bidirectional advance it ultimately formed a "pouch" divided by a purse string–like constriction at the point of origin in the wall of the bronchus. It was surrounded by a capsule of connective tissue, which was covered in the endobronchial segment by the bronchial mucosa.

Some observers identified still another type, the intramural, said to be strictly confined to the bronchial wall which it infiltrated.

In the early stages the adenoma appears as a wartlike prominence, usually firm and sessile; in the advanced stage it becomes pedunculated, sometimes assuming a pyriform shape, suspended and hanging by its constricted neck like a clapper of a bell. Its tendency to project upward is due to the expulsive effort of coughing.

Early observers considered bronchiogenic adenoma a slow-growing, benign new growth. The opinion of recent investigators is divided between those who stated that it is a benign neoplasm and those who considered it as potentially malignant. Adams and his associates [13] found in 1 of their cases a metastasis in the vertebral bone marrow, in another in the bronchial lymph node and in still another in the mediastinal lymph node and the liver. In Anderson's [14] case, tumor cells

8. Morlock, H. V., and Pinchin, A. J. S.: Brit. M. J. 1:911, 1933.

9. Foster-Carter, A. F.: Quart. J. Med. 10:139, 1941.

10. Kramer, R., and Som, M. L.: Ann. Otol., Rhin. & Laryng. 44:861, 1935.

11. Lowry, T., and Rigler, L. G.: Radiology 43:213, 1944.

12. Clerf, L. H., and Bucher, C. J.: Ann. Otol., Rhin. & Laryng. 51:836, 1942.

13. Adams, W. E.; Steiner, P. E., and Bloch, R. G.: Malignant Adenoma of Lung: Carcinoma-like Tumors with Long Clinical Course, Surgery 11:503 (April) 1942.

14. Anderson, W. M.: Bronchial Adenoma with Metastasis to Liver, J. Thoracic Surg. 12:351 (April) 1943.

extended between the bronchial cartilages and involved the entire thickness of the bronchial wall; they invaded several perivascular and peribronchial lymphatic vessels near the periphery of the growth and also the liver.

The occurrence of metastases, while extremely rare, is nevertheless puzzling, because the histologic structure of the tumor is that of a benign new growth. Its cells are uniformly the size of a lymphocyte or a plasma cell, with a somewhat oval nucleus and a narrow rim of cytoplasm. The arrangement of the cells is orderly, usually forming tubules without lumens or with barely noticeable lumens. The stroma is delicate, containing occasional slits lined with endothelial-like cells. In some cases of advanced metastases the stroma becomes dense, showing areas of ossification. Mitotic figures are rarely if ever found even in the adenomas which have metastasized to distant organs. Likewise, the infiltration of the stroma with lymphocytes, so characteristic of malignant tumors, is entirely lacking in bronchiogenic adenoma. Finally, adenomas are as a rule surrounded by a connective tissue capsule.

It is significant that the metastases found in a few cases were minute, sometimes microscopic and confined to only one or two organs, and they occurred in persons whose disease was of many years' duration. In cancer, it has been noticed, metastases often occur in inverse ratio to the tempo of the new growth; the slower the growth, the more widespread are the metastases.

Malignancy involves multiple factors, such as recurrence of growth after removal, metastases, radiosensitivity and constitutional symptoms, to mention but a few. Patients with bronchiogenic adenoma displayed none of the characteristics associated with malignant disease. Their ailment was protracted over many years, and the metastases were minute and few and were discovered accidentally at the postmortem examination. After the complete removal of the tumor the patients recovered.

At the Massachusetts General Hospital, of 175 cases of pulmonary tumors bronchial adenomas were found in 17, or 10 per cent. Fifteen (88 per cent) of the 17 patients were living and asymptomatic from three to five years later. Of 155 patients with carcinoma of the bronchus, only 5, or 3 per cent, were alive for the same period. Of 28 patients in whom the carcinoma had been removed surgically, only 3 (11 per cent) have a chance of five years' survival, while, of 11 patients in whom the adenoma had been removed surgically, 10 (90 per cent) were living and none revealed signs of malignant disease.

The histogenesis of the adenoma was traced by some observers to the cells lining the ducts of the bronchial glands and by others to oncocytes, epithelial cells resembling those of the organ in which they are found and
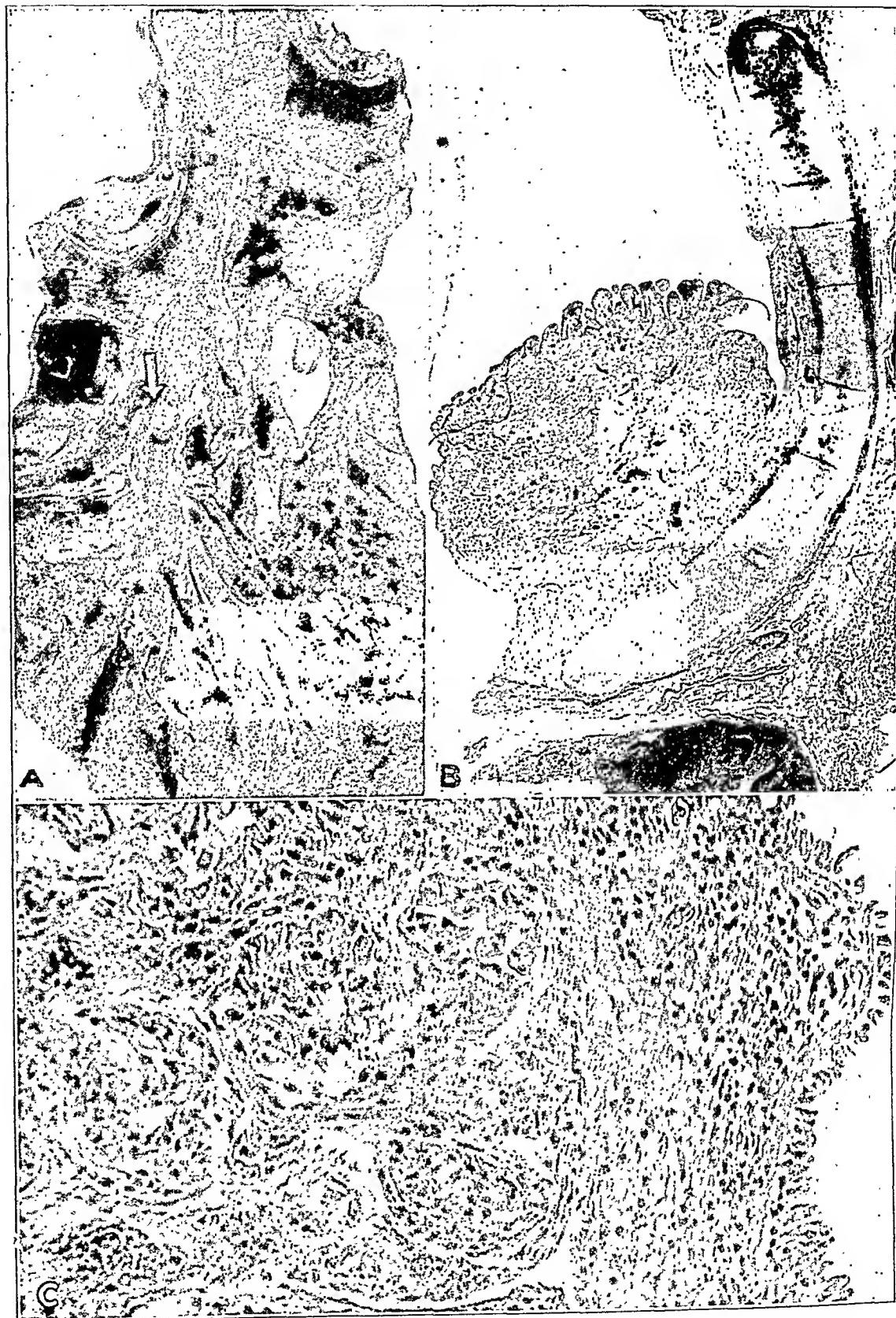
Fig. 1 (case 1).—*A*, polypoid endobronchial adenoma protruding into the bronchial lumen (arrow). *B*, cut surface of the tumor. *C*, histologic structure.

differing from them in size and in the presence of cytoplasmic acidophilic granules and deeply stained pyknotic nuclei (Stout [15]).

Womack and Graham [16] stated that bronchiogenic adenomas have their origin in anlages that have failed to develop normally. They stated: "These tumors resemble fetal pulmonary tissue. . . . they result from the failure of embryonic bronchial buds to develop into normal [bronchial] structures." In their opinion there exists a similarity of behavior and "in some respects" of origin of bronchial adenomas to the mixed tumors of the parotid gland, and as such the bronchial tumors are designated as mixed tumors of the lungs.

There are two possible sources for the origin of bronchial adenomas: (1) the bronchial mucous glands and (2) the basal cells of the bronchial mucous membrane. In the case of involvement of the mucous glands the tumor cells resemble the secreting cells of the gland—large polygonal cells with a wide rim of cytoplasm containing acidophilic granules and deeply stained nuclei. A case of this variety is herein presented.

CASE 1.—*History*.—The past history of the patient, aged 57, was irrelevant, and his present illness was that of hypertension and hypertensive cardiac disease, to which he succumbed. At necropsy the adenoma was found in the lower part of the left bronchus, at the point of its division into the upper and lower branches. It represented a round, smooth, grayish polypoid elevation protruding into the bronchial lumen, constricted at the base. It measured 1 cm. in diameter (fig. 1 *A* and *B*). Under the microscope it was composed of clustered alveoli made up of large polygonal cells with a finely granular acid-staining cytoplasm and a round or oval nucleus (fig. 1 *C*). The similarity of these cells to the aforementioned oncocytes is noteworthy. The stroma is made up of loose edematous connective tissue and numerous thin-walled channels filled with red cells. The tumor is surrounded by a collagenous capsule covered by a layer of bronchial epithelium undergoing metaplastic transformation.

It would appear that in this case the polypoid "excrescence," to use Laennec's term, took origin in the cells of the mucous glands.[17] However, by far the commoner source for the genesis of these tumors is the basal cells of the bronchial mucosa. These cells, found in clusters interspersed between the columnar and the mucous (goblet) cells, represent a dynamic unit, playing a role in regenerative and fibrogenic processes taking place in the lung. That this cell is the mother cell for bronchiogenic carcinoma is now universally accepted.[18]

15. Stout, A. P.: Cellular Origin of Bronchial Adenoma, Arch. Path. **35**:803 (June) 1943.

16. Womack, N., and Graham, E. A.: Mixed Tumors of the Lung, Arch. Path. **26**:165 (July) 1938.

17. Fried, B. M.: Adenoma of Bronchial Mucous Glands, Arch. Otolaryng. **20**:375 (Sept.) 1934.

18. Fried, B. M.: Primary Carcinoma of the Lung, Baltimore, Williams & Wilkins Company, 1932, p. 27.

The cells which make up bronchiogenic adenoma closely resemble basal cells. It is often possible to trace a connection between these cells and the tumor, although failure to find such a liaison does not invalidate the assertion of such a genetic relationship. Thus, it is well established that carcinoid tumors of the bowel originate from the epithelial cells of the Lieberkühn's crypts by cellular sprouting; however, with the advance of the tumor the connecting bridge vanishes.

DIAGNOSIS

In another section appears the statement that bronchiogenic adenoma has been compared with an iceberg, since only part of it is visible on the surface, and, like an iceberg, its advance is extremely slow. Cases are on record in which symptoms existed for decades. That there is a "preclinical" asymptomatic period goes without saying. Early complaints are usually those of a cough productive of mucoid sputum occasionally streaked with blood. The ominous symptom, however, is the occurrence of hemoptysis, which is characterized by abruptness and copiousness. Carcinoma of the lung, too, produces hemorrhages, but they are rarely abundant. The source of bleeding has been traced to ruptured thin-walled blood vessels which abound in polypoid adenomas. In the performance of biopsies it has been noticed that, unlike bronchiogenic carcinoma, adenoma bleeds profusely, the bleeding reaching at times a dangerous point.

In the past the disease had been diagnosed as tuberculosis, and patients were treated accordingly. Cases 2 and 3 are illustrative. Further in its course the symptomatology is dominated by the increasing size of the endobronchial growth, causing occlusion of the bronchial lumen. It is well to consider two phases: (1) preobstructive or partially obstructive and (2) obstructive.

In the first phase, in addition to cough and bleeding, a wheeze in the chest is heard on auscultation (heard best with the patient's mouth open), often by the patient himself. Not infrequently there is soreness of the chest on the side of the affected bronchus. Although not completely shut off from the ingress of air, the lung loses its usual resistance and readily becomes a prey to infection; the patients suffer sporadically from "colds," with elevation of temperature (recurrent "pneumonia"). Bronchial stenosis, whether caused by a tuberculous infection or a malignant or benign neoplasm, often induces stagnation, with the formation of a thick mucopurulent secretion plugging the bronchial lumen. The bouts of fever, lasting as long as this condition persists, are usually due to the obstruction. When the plug is removed spontaneously or with the bronchoscope, the condition clears up, only to recur with another obstructive episode; hence the recurrent pneumonic attacks.

When the obstruction becomes permanent, the segment of the lung distal to it becomes atelectatic and infected with pyogens, inducing pneumonitis, bronchiectasis, abscess and empyema.

Bronchostenosis and bronchial obstruction have been recognized for the past ten to fifteen years. Older clinicians (as well as pathologists), unaware of this phenomenon, focused attention on the parenchyma of the lung, which they treated without effect. Patients usually succumbed to complications. Indeed, early recognition of the source of the trouble followed by proper therapy is life saving.

That the adenoma has a tendency to affect larger bronchi (accessible to the bronchoscope) was mentioned in the introductory paragraphs. From a series of collected cases it would appear that it is encountered oftener on the right side. Of 217 cases from the literature, it occurred on the right side in 127, or 58.5 per cent, and on the left in 90, or 41.5 per cent. The lower lobe seems to be affected oftener than the upper.

The highest incidence of the disease is observed in the third and fourth decades, but persons in other age periods are not immune. According to Foster-Carter,[9] the majority of adenomas are recognized in patients between the ages of 30 and 40. Kramer and Som [10] observed an adenoma in a boy of 13, but 61 per cent of their patients were between the ages of 21 and 38. Jones and his associates [19] reported a case of an adenoma of the right main bronchus in a boy of 10 years. The boy died during a bronchoscopic examination. Of 123 cases culled from the available literature, 109 affected persons were under 50, and only 14 were above that age. It may be observed that bronchiogenic adenoma is but rarely seen at the age period when bronchiogenic carcinoma occurs most frequently.

Of interest, too, in this connection is the sex incidence. Of 160 cases, 71, or 44.25 per cent, occurred in men, and 89, or 55.75 per cent, occurred in women. These figures are of particular significance when compared with those found in cases of bronchiogenic carcinoma—80 per cent in men and only 20 per cent in women.

Bronchoscopy.—In the introductory paragraphs it was stated that the tumor has the aspect of a pouch constricted in the middle in an hour-glass fashion; at the point of constriction it is astride on the bronchial wall, one segment advancing toward the lung and the other toward the bronchial lumen. The adenoma was also likened to an iceberg, one portion of which (endobronchial) is on the surface while the other (intrapulmonary) is submerged. It is thus apparent that, while the bronchoscopist is not in a position to ascertain the extent of the lesion, he is able to point out the diagnosis and remove tissue for microscopic study. The bronchoscopist is also in a position to remove the mucous

19. Jones. R.; Mackenzie, K. W., and Biddle, E.: Brit. J. Tuberc. **37**:113, 1943.

plug occluding the bronchial lumen, thus facilitating reaeration of the atelectatic portion of the lung before infection has set in.

Roentgenography.—Modern methods of bronchography with the use of an opaque substance reveal the location of the intrabronchial growth. By the use of tomography the intrapulmonary tumor is visualized as a round, dense shadow with well defined borders characteristic of benign tumors.

TREATMENT

With the advent of the recent concept of bronchiogenic adenoma, notions of its treatment have undergone changes. One no longer considers the treatment of the visible portion of the tumor with radium, forceps, electrocoagulation or aspiration alone sufficient to eradicate the disease. Two illustrative cases are incorporated in this report. The patient in case 2 received fourteen bronchoscopic treatments during a period of seven years, without result. She ultimately underwent a lobectomy, with the removal of a sizable intrapulmonary tumor (fig. 2). The patient in case 3 is still under observation but it is feared that she too will meet the same fate.

That some tumors are confined uniquely to the bronchial lumen has been demonstrated by Jackson, and case 1 in the present series is illustrative in this respect (fig. 1). Such tumors disappear under local treatment.

Lobectomy or pneumonectomy is resorted to in instances when the size and sessile attachment of the adenoma render its bronchoscopic removal impossible and also when putrid infection has set in. Those who state that bronchiogenic adenoma is potentially malignant and that most of them ultimately become cancerous advise removal of the lobe or of the entire lung the moment one arrives at the diagnosis.

REPORT OF CASES

CASE 2.—*History.*—A woman of 39 years was admitted to the hospital in 1937, complaining of pain at the bases of both lungs. Her past, family and marital histories were noncontributory. She had been well until 1933, when she contracted a severe "cold" accompanied with a stubborn cough. During a coughing spell she expectorated about a glassful of bright red blood, and a few days later another hemoptysis occurred, amounting to about 2 glassfuls.

Roentgenographic examination showed moderate cylindric dilatation of the bronchi at the bases. The sputum was negative for tubercle bacilli. She was discharged from the hospital after several weeks, with the diagnosis of pulmonary tuberculosis.

Although her cough abated, expectoration of blood persisted. On fluoroscopic examination a "shadow at the base of the left lung" was noticed. Pain in the lower part of the chest persisted as well as the sporadic hemoptyses, which at times amounted to half a cupful. She lost some weight. After a profuse hemoptysis, she was admitted to the Montefiore Hospital.

Bronchoscopy performed in May 1937 disclosed a readily bleeding purplish mass on the posterolateral branch of the bronchus of the lower lobe of the right lung.

Roentgenologic examination revealed within the pulmonary parenchyma a pear-shaped mass about 5 cm. in diameter; it was situated on the right side, external to the cardiac shadow. A roentgenographic examination performed seven months later, following the injection of iodized poppy seed oil, showed that the oil penetrated with difficulty into some branch bronchi of the lower lobe in the neighborhood of the mass. One branch bronchus in the vicinity was completely obstructed, and the lung around it showed no aeration.

The diagnosis was adenoma of the bronchus of the lower lobe of the right lung. The patient was treated by diathermy coagulation through the bronchoscope.

Interval Course.—She was discharged from the hospital improved, but soon small hemoptyses recurred. At times blood kept oozing for hours. While bronchoscopically the bronchial lumen was virtually patent, roentgenologically the tumor within the pulmonary parenchyma showed steady growth. From 1937 to 1944 the patient was admitted to the hospital fourteen times, receiving treatment through the bronchoscope. Hemoptyses could not be controlled. In 1944 it was finally decided to perform a lobectomy.

Lobectomy.—At operation the pleura overlying the tumor showed no inflammatory changes; the pleural cavity was patent, and most of the lung was crepitant and of normal color. A solitary tumor, lobulated, soft and encapsulated, measuring 6.5 by 5.0 by 4.5 cm., was found in the center of the lobe (fig. 2 A). About 0.5 centimeter from the mass the main lobar bronchus showed a defect filled with tumor, which apparently originated here. There was a moderate bronchial dilatation.

The tumor (fig. 2 B) was made up of columns of uniform cells separated by extremely thin connective tissue. No mitoses were found. The stroma was vascular, and the blood vessels were often engorged with blood. In the vicinity of the growth, tumor cells were seen within the wall of a compressed bronchus, but no tumor was found elsewhere. A comparative study of the histologic nature of the tumor with that of the biopsy specimen removed eight years previously proved them to be identical.

Comment.—The case is characteristic in the onset of the disease with cough and bloody expectoration and in its protracted course. Although the sputum was invariably negative for tubercle bacilli, the diagnosis of tuberculosis was entertained until the bronchoscopic examination revealed the nature of the disease. As the tumor grew endobronchially and within the pulmonary parenchyma its bronchoscopic removal was not alone sufficient to cure the disease. However, it was important in keeping the bronchial lumen patent, thus preventing atelectasis and putrid infection of the lung. About twelve years after the onset of symptoms lobectomy was resorted to, resulting in a cure.

The patient was readmitted to the hospital two years later for carcinoma of the breast. It would appear then that, although she had lurking possibilities for carcinogenesis, neither time nor repeated trauma had led to the transformation of the benign adenoma into a malignant carcinoma.

Case 3.—*History.*—A single woman, a clerk aged 27, dated her illness back to February 1940, when she became aware of pain in the chest, cough, night sweats
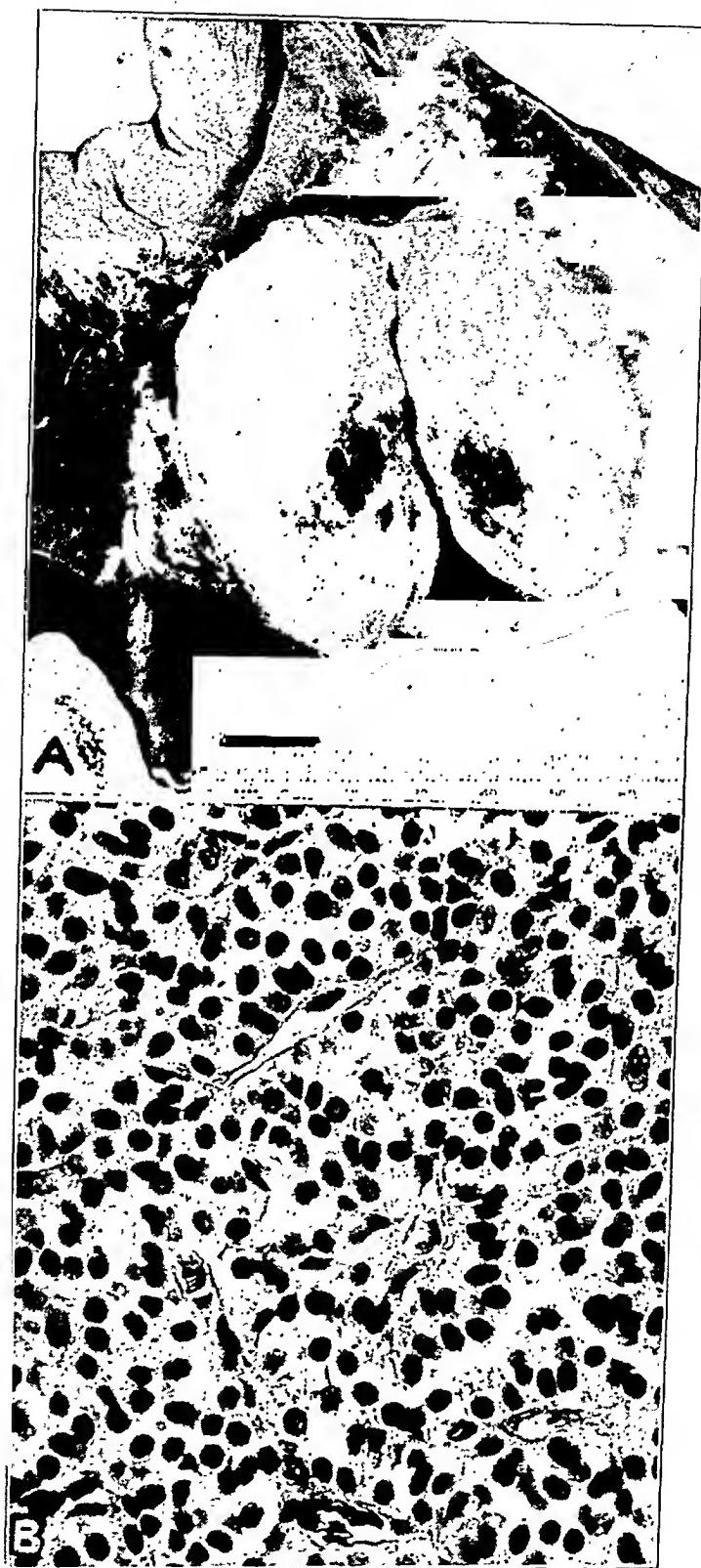
Fig. 2 (case 2).—*A*, cut surface of the adenoma removed at operation. *B*, histologic structure of the tumor.

and loss of weight and the fact that her sputum was blood streaked on several occasions. The diagnosis of pulmonary tuberculosis was made; she was given rest in bed, which led to her improvement until February 1941, when small hemoptyses recurred. The diagnosis of tuberculosis was reaffirmed, and a futile attempt to induce pneumothorax was made. She was again ordered to bed and remained bedridden until September, when she was transferred to a sanatorium for tuberculous patients. Her sputum remained free from tubercle bacilli. For several months she had perceived a wheezing sound in her chest.

On admission to the Montefiore Hospital she appeared to be well nourished. Loud sonorous rales were heard throughout the chest. The vital capacity was 2,600 and the sedimentation rate 40.

Roentgenologic examination revealed a wedge-shaped shadow, with its base at the mediastinum; it extended from the right hilus toward the periphery at the
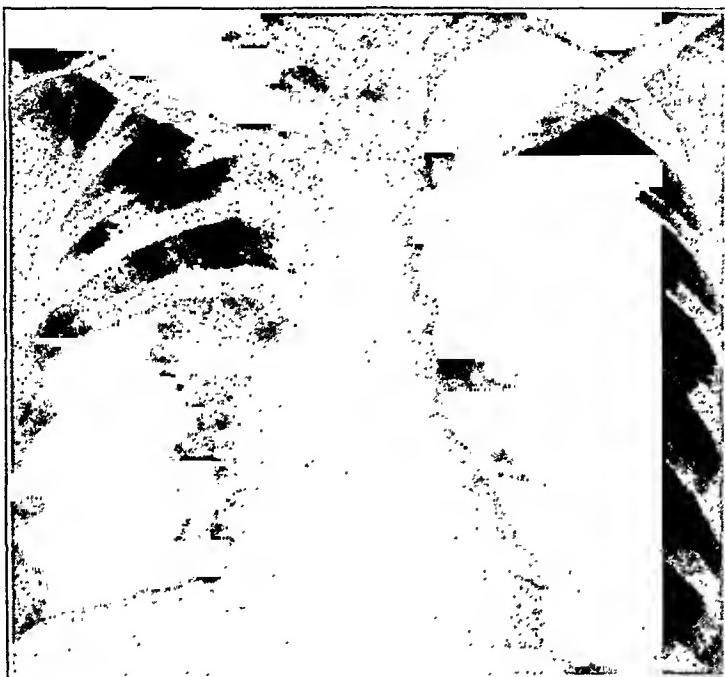
Fig. 3 (case 3).—Roentgenogram of the lungs, showing a triangular shadow on the right side due to atelectasis caused by obstruction of the bronchus.

level of the third rib anteriorly (fig. 3). There was some shrinkage of the upper lobe of the right lung; the trachea was retracted to the right side, and the right lung showed reduced expansion. The homolateral leaf of the diaphragm was elevated. The findings were indicative of lobar atelectasis due to stenosis of the bronchus of the upper lobe. The impression was that one was dealing with moderately advanced pulmonary tuberculosis accompanied with tuberculous endo-bronchitis.

On bronchoscopic examination the right bronchus was occluded by a smooth mass, which apparently originated in the posterior wall of the upper lobe of the right lung. A biopsy specimen was removed, which on histologic examination showed the tumor to be an exact replica of that in case 2.

Comment.—While in case 2 the disease had been observed in the preobstructive phase, in this case obstruction was quasicomplete when

the patient came under observation. She had as yet escaped the sequel of bronchostenosis, such as putrid infection of the lung or empyema. She is being treated bronchoscopically, but it is feared that eventually a
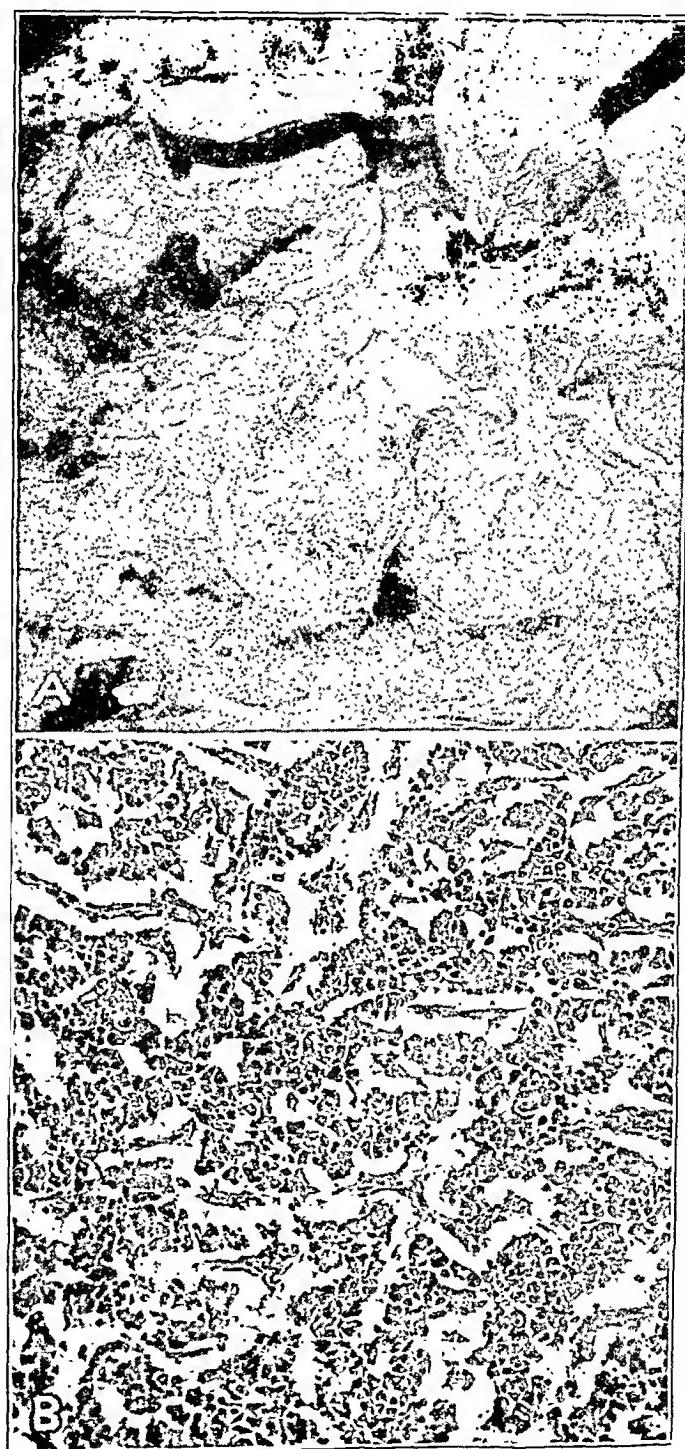
Fig. 4 (case 4).—*A*, cut surface of the adenoma surrounded by a capsule. *B*, histologic structure of the tumor.

lobectomy or pneumonectomy will have to be performed. Unlike the patient in case 2, in which the diagnosis of tuberculosis was entertained for a short time only, this patient was treated for tuberculosis for nearly two years.

CASE 4.—*History.*—Examination of a woman of 68 years revealed a dense shadow at the base of her right lung, diagnosed as bronchogenic carcinoma. Six years previously she had noticed blood-streaked sputum and occasional hemoptysis, and they had persisted for a few years. Reexamination two years later revealed the shadow unchanged, and as it moved with respiration it was interpreted as a benign tumor or possibly an organized abscess of the lung. Two years later she died of a cardiac condition.

At autopsy the lower lobe of the right lung was shrunken and distorted, and the pleura along the inferior border was thickened and deeply retracted. A firm mass was felt posteriorly in the region of the lower and middle lobes (fig. 4 *A*), and the rest of the lung was noncrepitant. The mass (3.5 by 4.5 cm.) was lodged in the lower portion of the lung posteromedially. It arose from the main bronchus to the lower lobe, about 3 cm. from the carina, completely obliterating the bronchial lumen. The branches to the lower lobe were almost completely obliterated and replaced by tumor. Only fragments of cartilage remained in the bronchial wall in this region.

The tumor grew within the bronchial lumen and within the parenchyma of the lung. It was sharply demarcated, encapsulated and hard as stone. The larger bronchial branches and the blood vessels in the vicinity of the tumor were merely pushed aside and compressed but not eroded or occluded. The bronchus to the middle lobe too was compressed but not obliterated, and the lobe was partially atelectatic. No metastases were present. The histologic nature of the tumor shown in figure 4 *B* is that of a solid adenoma of the bronchus. It is benign by all criteria.

Comment.—If one is to rely on the patient's story, except for hemoptyses and blood-streaked sputum she experienced no other ill effects from the neoplasm.

CASE 5.—*History.*—A pharmacist of 65 years was seen for the first time in June 1944 for pain in the dorsal part of the spine. His past history was irrelevant, and the physical examination revealed nothing worthy of note. On roentgenologic examination the spine showed no abnormalities, but a well circumscribed mass measuring about 6 cm. in diameter was noticed in the upper lobe of the right lung (fig. 5). The diagnosis of bronchiogenic carcinoma was made, and the patient was subjected to radiation therapy. While under treatment a pulmonary infection developed, to which he succumbed.

At necropsy a tumor 6 cm. in diameter was found in the upper lobe of the right lung posteriorly. It surrounded a secondary branch of the bronchus of the upper lobe without, however, narrowing the bronchial lumen. The bronchial wall was normal for about 3 cm., after which it abruptly closed, the bronchus being buried within the mass which enveloped it. The lungs showed considerable fibrosis. The tracheobronchial lymph nodes contained no tumor.

On microscopic examination the tumor was partitioned into lobules resembling those of the pancreas or the salivary gland. The cells were wholly degenerated, but their structure could be identified as polygonal or roughly round with round

nuclei. The new growth was surrounded by a capsule, the outer coat of which showed lamellary hyalinization, while the inner coat was densely hyalinized. Beyond the hyalin there was a ring of young fibrous tissue, possibly the reaction to the 7,000 r delivered to the patient's chest. No tumor was found elsewhere.

Comment.—Here is an instance of a wholly asymptomatic adenoma. The bronchial occlusion led to no known pulmonary complications. Apparently the tumor grew slowly, and with its capsule hyalinized it was entirely shut off from the circulation and became degenerated.

CASE 6.—*History.*—A married woman, aged 64, was in good health until she was 48 years, when diabetes, hypertension and hypertensive cardiovascular disease
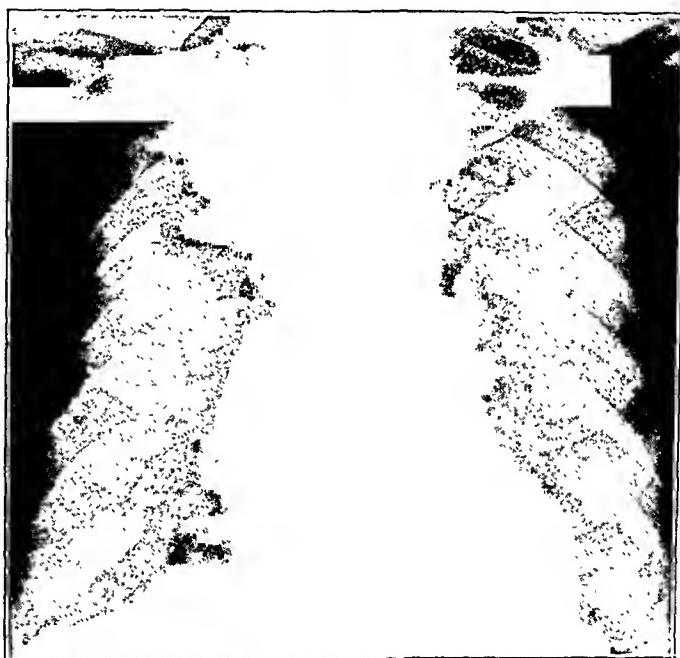
Fig. 5 (case 5).—Roentgenogram showing bronchiogenic adenoma in the upper lobe of the right lung.

developed. On routine examination of her chest a round, sharply circumscribed area of density, 2 cm. in diameter, was noticed in the middle zone of the right lung anteriorly. The suggestion was made that it might be a metastasis, a tuberculous infiltration, an infarct or a bronchiogenic carcinoma (fig. 6 B).

At necropsy an encapsulated tumor measuring 2 cm. in diameter was found at the base of the upper lobe of the right lung (fig. 6 A). It arose in the mucosa of a small bronchus to the upper lobe. No metastases were found in the lymph nodes or in the viscera.

Comment.—In this case the adenoma was accidentally discovered during a roentgenologic examination. If in the past the tumor had caused disturbances they were apparently so mild as to be disregarded by the patient.

CONCLUDING NOTE

Unlike bronchiogenic carcinoma, adenoma of the bronchus represents a relatively simple diagnostic problem. Of paramount importance is the assertion that the tumor is potentially malignant and that in most
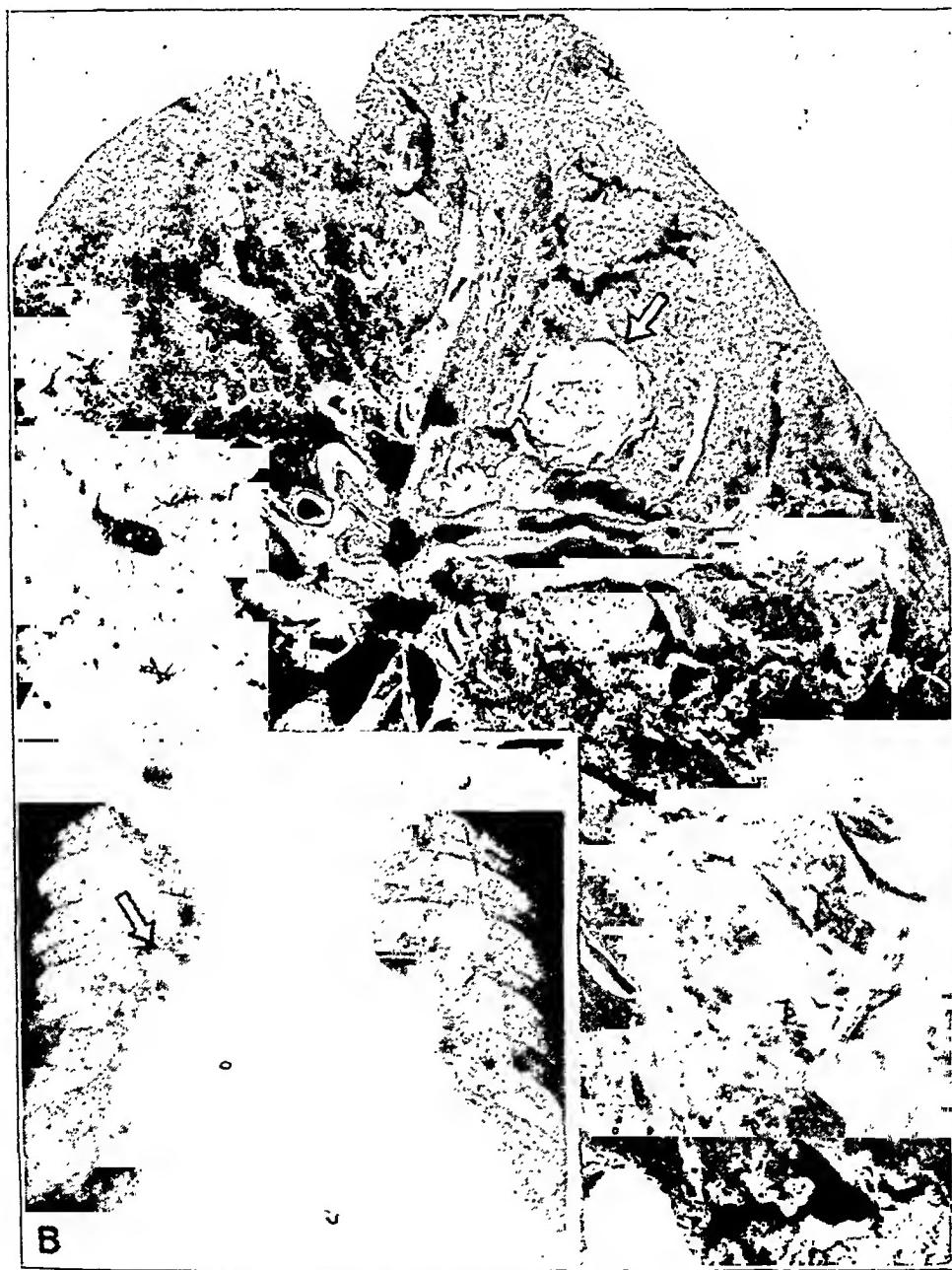
Fig. 6 (case 6).—*A*, cut surface of the lung, showing the circumscribed adenoma (arrow). *B*, roentgenogram showing the tumor in the right lung (arrow).

instances it "degenerates" into a bronchiogenic carcinoma. By some continental observers it has been defined as carcinoid and by others as basal cell carcinoma. It also has been stated that, while clinically it is benign, pathologically it is malignant (or semimalignant).

The view, however, that the adenoma is a benign tumor by nearly all criteria is gaining ground. Metastases have been observed in extremely few instances. They were few and minute and were discovered accidentally at the postmortem examination. No recurrences were observed following removal of the tumor which per se caused no deaths.

Not even locally (as some would have physicians believe) is the adenoma malignant. In its growth it may form a "bulge" but hardly ever a "break through." Indeed, the main characteristic of carcinoma, "schwerpunkt und aufrollen (break though and unfold)," is lacking in this tumor, which is surrounded by a capsule. The assertion that bronchiogenic adenoma often "degenerates" into bronchiogenic carcinoma has not been confirmed. The adenoma is, indeed, expansive but not invasive.

It is the commonest benign bronchial tumor, comprising from 6 to 12 per cent of all bronchial neoplasms. It is prevalent in patients in the third and fourth decades and occurs oftener in women and more frequently on the right side. It occurs in bronchi accessible to inspection with the bronchoscope and presumably easily diagnosed.

Therapy applied in the early stages eradicates the disease, while dilatoriness is fraught with dangerous complications, such as putrid abscess and bronchiectasis, pneumonitis and empyema.

PRIMARY HYPERTROPHY AND HYPERPLASIA OF THE PARATHYROID GLANDS ASSOCIATED WITH DUODENAL ULCER

Report of an Additional Case, with Special Reference to Metabolic, Gastrointestinal and Vascular Manifestations

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IN A PREVIOUS publication,[1] attention was called to the association of duodenal ulcer in 1 case with parathyroid adenoma and in a second case with primary hyperplasia of the parathyroid glands. In both cases the ingestion of large quantities of calcium and phosphorus in diets prescribed for the treatment of duodenal ulcer was associated with acute manifestations of hyperparathyroidism which terminated fatally. Since this report, a third case of probable hyperparathyroidism associated with duodenal ulcer has been observed. Primary hypertrophy and hyperplasia of the parathyroid glands were present in association with a well healed duodenal ulcer. In view of the diagnostic importance of gastrointestinal symptoms in hyperparathyroidism and because the coexistence of duodenal ulcer both obscures the diagnosis of hyperparathyroidism and complicates its treatment, this association deserves further emphasis. Furthermore, since primary hypertrophy of the parathyroid glands is uncommon, the finding of an additional case is noteworthy.

REPORT OF A CASE

The patient was a white man, aged 68 years, who was first seen at the Mayo Clinic in 1919, when posterior gastroenterostomy was performed because of duodenal ulcer. For many years thereafter he was reasonably well, but episodes of mild gastric distress continued to occur from time to time, most frequently in the spring or fall. He again registered at the clinic, on March 12, 1945, complaining of epigastric pain of four months' duration. Ingestion of food had been decreasingly effective in relieving the pain, and he stated that milk disagreed

with him. Anorexia and nausea had been present for six weeks; vomiting had occurred two weeks previously, and during the previous week it had occurred eight times, usually giving relief from nausea. No special diet had been observed. Constipation accompanied the appearance of epigastric pain. The patient had lost 25 pounds (11.3 Kg.).

In addition to the foregoing complaints, the patient had experienced certain symptoms referable to the skeletal system. For two to three years he had felt

Fig. 1.—Posterior view of the organs of the neck, demonstrating primary hypertrophy of the parathyroid glands. The esophagus has been opened. The left superior and right superior parathyroid glands are seen as well as the superior portions of both lobes of the thyroid.

pain in the right foot, occurring when he was walking or bearing weight. This pain extended from the right heel to the right hip, and there was occasionally pain in the left hip. For two years pain had been present in the ankles, knees and shoulders, and the patient had noticed stiffness and weakness. His family noticed that he appeared bent over when walking.

Physical examination revealed a tall, thin, elderly man. The pulse rate was 70 beats per minute. The blood pressure ranged from 130 to 140 mm. of mercury systolic and from 92 to 100 diastolic. A systolic aortic murmur was heard. All palpable vessels were much thickened, and radial sclerosis was pronounced. There was muscular atrophy, with wasting and weakness of all muscles of the arms and legs. The thoracic portion of the spinal column was moderately kyphotic. The prostate was moderately enlarged on palpation.

The examination of the urine revealed a specific gravity of 1.012, an acid reaction and the presence of albumin (grade 2; on the basis of 1 to 4, in which
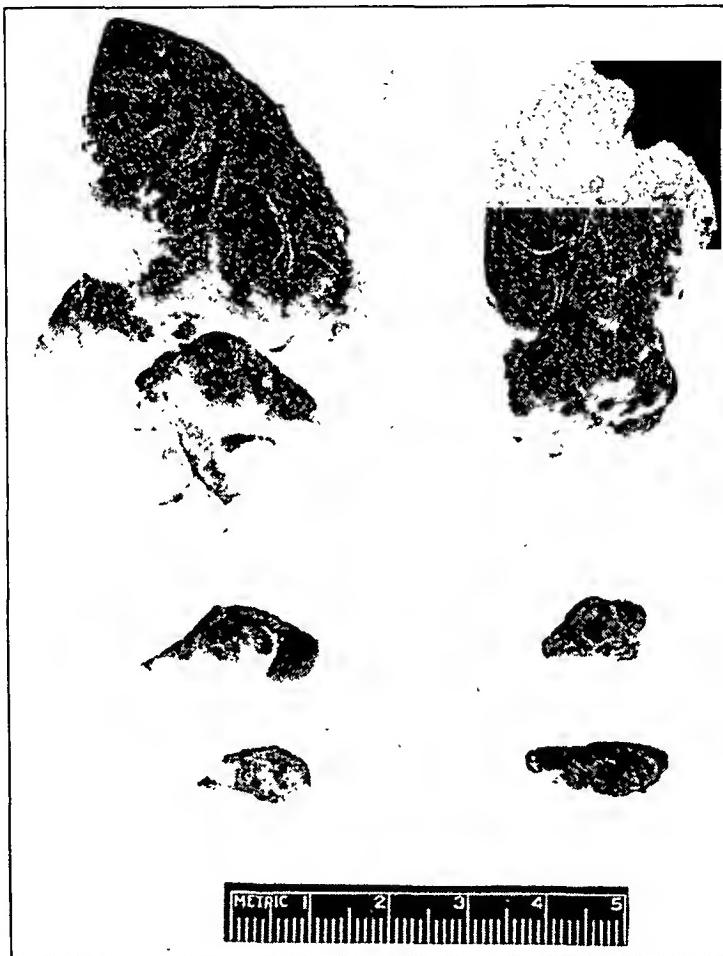
Fig. 2.—Primary hypertrophy of the parathyroid glands. Illustrated are the left superior, middle and inferior parathyroid glands and the right superior, middle and inferior parathyroid glands. Pseudopodal projections are seen from the left and right superior glands.

1 designates the mildest and 4 the severest condition). No sugar was found, and microscopic studies of sediment gave normal results. The concentration of hemoglobin was 13.1 Gm. per hundred cubic centimeters of blood; erythrocytes numbered 4,140,000 and leukocytes 10,000 in each cubic millimeter of blood. The routine flocculation test for syphilis gave negative results. Roentgenograms revealed scoliosis and kyphosis in the upper part of the thoracic area, an old duodenal ulcer and a diverticulum of the second portion of the duodenum.

The patient was hospitalized, and a modified diet for patients with ulcer was prescribed, which contained 1.7 Gm. of calcium and 1.4 Gm. of phosphorus augmented daily with aluminum phosphate gel. Despite treatment, moderate epigastric distress was still present at the time of his dismissal on March 28, 1945. While a gastrojejunal ulcer was suspected, it was observed that the typical shift of pain to the left had not occurred.

At the time of the patient's next examination, on Oct. 1, 1945, he complained mainly of blueness of the great toe of the left foot, of one week's duration. Generalized pruritus, nervousness and insomnia had been present for four weeks. In the interim between examinations vomiting three to four times weekly had occurred from June to September, and pronounced polydipsia and polyuria had been present during this time. Increasing pain in the right leg and weakness had been present for two weeks. Mental confusion began one to two weeks preceding this admission.

The results of physical examination were the same, except for gangrene of the great toe of the left foot. Dorsalis pedis and posterior tibial arterial pulsations were absent bilaterally, while popliteal and femoral arterial pulsations were normal bilaterally.

Dimensions and Weights of Parathyroid Glands

	Dimensions, Cm.	Weight, Gm.
Right superior parathyroid...............	5.2 by 2.2 by 2.0	14.2
Right middle parathyroid................	1.2 by 0.5 by 0.5	0.55
Right inferior parathyroid...............	1.8 by 0.6 by 0.3	0.36
Left superior parathyroid................	7.2 by 4.5 by 2.8	30.9
Left middle parathyroid.................	2.2 by 1.0 by 0.9	1.45
Left inferior parathyroid...............	1.2 by 0.5 by 0.2	0.1
		47.56

The results of studies of the urine were unchanged. The concentration of hemoglobin was 7.5 Gm. per hundred cubic centimeters of blood; erythrocytes numbered 2,350,000 and leukocytes 15,600 in each cubic millimeter of blood. A roentgenologic examination of the thorax revealed prominence of the left ventricle. An electrocardiogram was normal except for premature auricular contractions. The concentration of urea was 182 mg., and that of cholesterol was 107 mg. per hundred cubic centimeters of blood. The fatty acids were 261 mg. and the total lipids were 368 mg. per hundred cubic centimeters of plasma.

Intravenous administration of dextrose was instituted, but progressive disorientation occurred, and on October 4, three days after his admission to the hospital, the patient became comatose. The concentration of urea rose to 258 mg. per hundred cubic centimeters of blood. Death occurred on October 5, four days after his final admission.

Observations at Necropsy.—At postmortem examination the following observations were deemed significant. There was definite hypertrophy of the parathyroid glands and supernumerary glands (figs. 1 and 2). The weights and measurements of the individual parathyroid glands are given in the table. The parathyroid glands were firm and brown. Pseudopodal projections were observed from the right superior parathyroid gland measuring 1.5 by 0.5 by 0.3 cm. and 1.0 by 1.0 by 0.4 cm. and from the left superior parathyroid measuring 2.7 by 1.7 by 1.0 cm. and 1.0 by 1.0 by 0.8 cm. Cysts were present in the left superior parathyroid gland, and small petechial hemorrhages were present over their

surfaces. The cut surface of this gland (fig. 3) revealed one large cystic area, measuring 2.0 by 2.2 by 1.8 cm., in the midportion of the gland, composed of smaller cystlike cavities, measuring 1 to 2 mm. in diameter and filled with blood. Small hemorrhagic cysts, measuring 0.3 and 0.5 cm. in diameter, were also present in the left superior parathyroid gland, and two cysts containing clear fluid and measuring 0.5 cm. and 0.2 cm. were present in the right superior parathyroid gland. The total mass of parathyroid tissue weighed 47.56 Gm.

The lungs revealed purulent bronchitis, grade 1. The heart was hypertrophic and weighed 506 Gm.

In the stomach there was an old posterior gastroenterostomy scar, the stoma of which measured 0.4 cm. in diameter. There were a healed jejunal ulcer and a healed duodenal ulcer. Diverticula were present in the duodenum and the sigmoid colon. The pancreas weighed 90 Gm. Throughout the pancreas there were multiple mulberry-shaped deposits of calcium which ranged in diameter from 0.4 cm. up to 2.0 cm. There was moderate dilatation of the pancreatic ducts.

Fig. 3.—The left superior and right superior parathyroid glands. One large and two small cysts with hemorrhage are present in the left superior gland.

The right kidney weighed 113 Gm. and the left kidney 145 Gm. Their surfaces were diffusely granular and contained parenchymatous cysts ranging from 0.5 to 3.8 cm. in diameter. The cut surfaces were brown, with small white regions in the medullae, measuring up to 1 mm. in diameter.

There was dry gangrene of the great toe of the left foot.

The histologic appearance of all the parathyroid glands was similar except for minor variations. The constant type of cell throughout was the large water-clear cell (fig. 4). The diameter of these cells varied from 8 to 38 microns, the large majority of the cells being from 18 to 22 microns. In most of the cells the nucleus was small, but in a few instances larger nuclei were observed. There was characteristic polarity of the nucleus, which frequently was located at the periphery of the cell. Mitotic figures were absent. The cytoplasm was clear except for a few eosinophilic granules in the periphery of some cells. Small deposits of glycogen were present in the cytoplasm of some of the cells. Mucin stains gave negative results, and frozen sections stained with sudan II did not disclose fat. In some sections the cells were arranged in solid sheets, but in most regions there was a tendency toward acinar arrangement with pseudoglandular formation. Adipose connective tissue cells were absent, and connective tissue stroma was for

the most part sparse. Blood vessels were numerous. Hemorrhage was present in some of the cystic regions observed in the left superior parathyroid gland. The microscopic appearance was typical of that described previously in cases of primary hypertrophy and hyperplasia of the parathyroid glands.
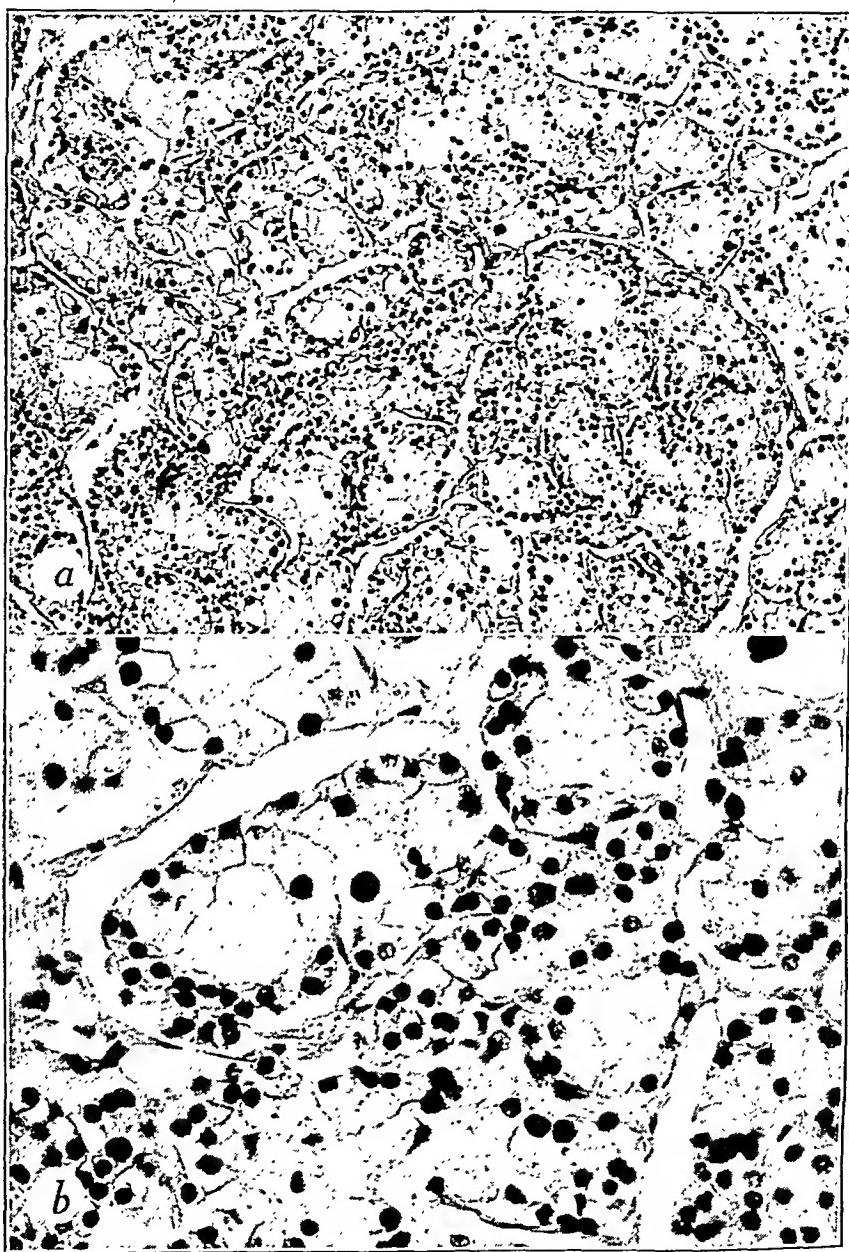
Fig. 4.—Parathyroid gland. *a,* typical appearance of primary hyperplasia, showing acinar grouping. In some regions the cells assumed the form of solid columns. × 120. *b,* higher magnification, showing the large *wasserhelle* cells with clear cytoplasm. Note polarity of the nuclei. × 350.

All sections of the thyroid gland were normal. The sections of the *lungs* were normal, but in the larger bronchi polymorphonuclear leukocytes were present.

In all sections of the pancreas there was decided dilatation of the ducts. Deposits of calcium were present within the ducts and throughout the parenchymal tissue. The acinar cells in the head of the pancreas were normal. In the tail of

Fig. 5.—*a*, kidney, showing nephrocalcinosis. Deposits of calcium are present in the interstitial tissue. × 85. *b*, deposits of calcium in tubules surrounding a glomerulus. × 250.

the pancreas, atrophy of the glandular elements was striking, with replacement by fibrous connective tissue. The islets were preserved.

In the kidney two distinct changes were noted. Most striking of these was widespread nephrocalcinosis (fig. 5). Deposits of calcium were observed in both

convoluted and collecting tubules, and in some instances these were associated with necrosis of the epithelial cells. Interstitial deposits of calcium were likewise present. In addition there was atrophy, as seen in arteriosclerotic kidneys. These
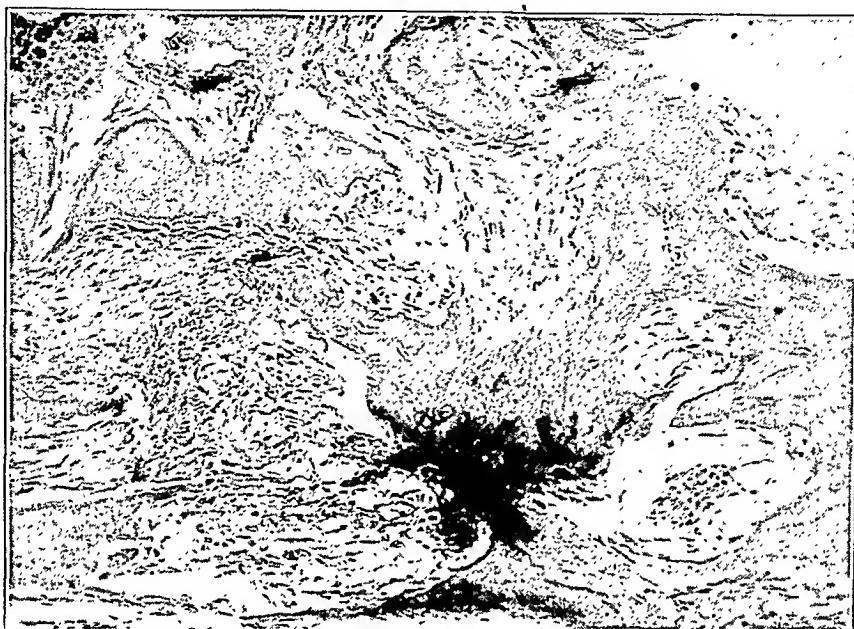
Fig. 6.—Section of a vertebra, showing fibrous change suggestive of osteitis fibrosa cystica. × 115.

Fig. 7.—Branch of a renal artery, illustrating deposits of calcium in the internal elastic lamina. × 300.

changes consisted of medial thickening of many small and medium-sized arteries, an occasional hyalinized glomerulus, atrophic tubules in some regions with dilated

tubules in others, swollen tubular epithelial cells and increase of interstitial tissue with lymphocytes.

In decalcified sections of the vertebrae (fig. 6) and ribs there was well marked osteitis fibrosa with small cysts. Osteoclasts were present in greatly increased numbers at the edges of the trabeculae of the bone.

Examinations of sections of the larger arteries (the aorta, renal, superior mesenteric, common and external iliac, right popliteal and coronary arteries) showed a moderate degree of patchy atheromatous degeneration and scattered small deposits of calcium in the medial coats. These changes were not remarkable or excessive for the patient's age. However, an unusual type of arterial lesion was seen in almost all the sections studied. This consisted, in every section, of one or more irregular patches of necrosis of the arterial wall, which were sometimes of considerable size. In these patches the cells of the muscular and fibrous tissue had lost their nuclei but retained their form and arrangement. Around the irregular margin of the necrotic patch was a fine, darkly stained line of calcium deposit. Otherwise, there was little or no calcium in the necrotic tissue. In some regions the necrotic patch involved the intima, and here the irregular boundary of calcium was seen in the internal elastic lamina (fig. 7).

Fig. 8.—Postmortem roentgenogram of the pancreas, showing multiple pancreatic calculi.

A review of the roentgenograms of the spinal column revealed mild demineralization, with coarsening and widening of the trabeculations of the vertebrae, consistent with hyperparathyroidism. Postmortem roentgenologic study of the kidneys disclosed diffuse calcification of the parenchyma and calcification of the main renal arteries and their smaller branches. A portion of each kidney was analyzed for calcium; the right kidney contained 3.43 mg. of calcium per gram of wet tissue and 16.74 mg. per gram of dry tissue; the left kidney contained 1.86 mg. of calcium per gram of wet tissue and 9.19 mg. per gram of dry tissue. A roentgenogram of the pancreas taken after death revealed extreme calcification (fig. 8). On analysis, one of the pancreatic calculi was found to contain only calcium carbonate.

COMMENT

Pathologic Considerations.—The parathyroid glands in this case demonstrated the typical appearance of "primary hypertrophy" of the parathyroids with characteristic pseudopodia. There were supernumerary parathyroids, and the possibility that they originated as pseudopodia from the main glands must be entertained. Cysts and hemorrhage were observed in the larger glands. Histologically, the large clear cell was

constant in all glands. The weight of the parathyroid tissue (47.56 Gm.) is the greatest recorded in instances of primary hypertrophy and hyperplasia.

Primary hypertrophy or hyperplasia of the parathyroid glands, as illustrated by this case, must not be confused with secondary hyperplasia of the parathyroid glands occurring in cases of long-standing renal insufficiency.[2] In cases of secondary hyperplasia, enlargement does not reach the degree observed in this case, and histologically the gland is composed of chief cells, alone or in combination with oxyphil cells. In primary hyperplasia the histologic examination discloses only large water-clear (*wasserhelle*) cells.

Primary hyperplasia has been observed infrequently. In the large series of cases of primary hyperparathyroidism observed at the Massachusetts General Hospital by Albright [3] and Cope [4] and their colleagues, it has occurred eight times. Albright has suggested that the process represents hypertrophy rather than hyperplasia, because in his material he found that the mean size of the cell was increased sufficiently to account for the increased mass of the glands without assuming any increase in the number of cells. However, in this case, as in the case of primary hyperplasia previously reported from the Mayo Clinic, the increased size of the cell appears totally inadequate to account for the weight of the glands. In the present instance the weight, 47.56 Gm., represents an increase of approximately four hundred times over the normal weight of the parathyroids. We, therefore, feel that "hyperplasia" is a more accurate designation for this process than "hypertrophy."

The lesions in the larger arteries are worthy of some comment. The peculiar regions of necrosis surrounded by a fine boundary of calcium had the appearance of infarcts of the arterial wall, and all appeared to be of approximately the same age. It is uncertain whether the hypercalcemia produced these lesions or whether the calcium was merely being deposited in a region of degenerated tissue, as so often occurs in patients without parathyroid disease. Inasmuch as the lesions involved the intima and internal elastic lamina in some instances, it is obvious that they might be favorable sites for the development of thrombosis. This

2. Castleman, B., and Mallory, T. B.: Parathyroid Hyperplasia in Chronic Renal Insufficiency, Am. J. Path. **13**:553-574 (July) 1937; The Pathology of the Parathyroid Gland in Hyperparathyroidism: A Study of Twenty-Five Cases, ibid. **11**:1-72 (Jan.) 1935.

3. Albright, F.: The Parathyroids: Physiology and Therapeutics, J. A. M. A. **117**:527-533 (Aug. 16) 1941.

4. Cope, O.: Hyperparathyroidism: Sixty-seven Cases in Ten Years, J. Missouri M. A. **39**:273-278 (Sept.) 1942; Hyperparathyroidism: The Significance of Generalized Hyperplasia; Report of the Seventh Case, Clinics **1**:1168-1178 (Feb.) 1943.

is the probable explanation for the occlusion of the arteries of the legs and the gangrene of the great toe of the left foot. These arterial lesions represent a somewhat different mechanism from the usual type of arteriosclerosis obliterans which is seen in elderly persons who have extensive atheroma.

The Diagnosis of Hyperparathyroidism.—The possibility that this patient had hyperparathyroidism was not considered during life. Since the blood and urine were not analyzed for calcium or phosphorus, chemical confirmation of this diagnosis was not obtained. When the record is reviewed in the light of the postmortem observations, however, the existence of primary hyperparathyroidism may be assumed with considerable assurance. So far as is known, hyperplasia of the parathyroids involving *wasserhelle* cells is always associated with primary hyperparathyroidism. The finding at necropsy of nephrocalcinosis and changes in the bones characteristic of osteitis fibrosa cystica further confirms this diagnosis.

In retrospect, a good many of the symptoms presented by the patient could be ascribed to hyperparathyroidism. The history of skeletal pain for three years suggested osseous involvement, and the roentgenograms showed mild but definite changes which were compatible with hyperparathyroidism but not pathognomonic of it. Epigastric pain, constipation, anorexia, vomiting and loss of weight, which were present during the last year of life, probably resulted from hypercalcemia; the weakness and mental confusion may have had the same significance. The polyuria and polydipsia, as well as the terminal azotemia, are consistent with the renal manifestations of hyperparathyroidism.

The clinical diagnosis of hyperparathyroidism depends on the demonstration of an increased concentration of calcium and a reduced concentration of phosphorus in the serum together with an increased excretion of calcium in the urine, although these abnormalities may be obscured or effaced in the presence of severe and protracted renal insufficiency. The clinician is usually induced to seek chemical proof of abnormal function of the parathyroids only when his suspicion is aroused by some spectacular manifestation of hyperparathyroidism. For many years the diagnosis was made only in cases in which the far advanced manifestations of skeletal demineralization known as von Recklinghausen's osteitis fibrosa cystica were present. In more recent years, as a result of the studies of Albright and his colleagues,[5] suspicion of hyperparathyroidism has been aroused by the occurrence of renal stones.

5. Albright, F.; Aub, J. C., and Bauer, W.: Hyperparathyroidism: A Common and Polymorphic Condition as Illustrated by Seventeen Proved Cases from One Clinic, J. A. M. A. **102**:1276-1287 (April 21) 1934. Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Studies on the Physiology of the Parathyroid Glands: IV. Renal Complications of Hyperparathyroidism, Am. J. M. Sc. **187**:49-65 (Jan.) 1934.

It is becoming apparent, however, that hyperparathyroidism may exist, perhaps for a long time, without producing either conspicuous skeletal symptoms or renal stones. Albright[6] has reported 1 case in which hyperparathyroidism was suspected because of pronounced weakness and lassitude. Careful examination disclosed minimal demineralization of the skeleton, but chemical criteria of hyperparathyroidism were found and an adenoma was removed at operation. One of us[7] has observed a case in which hypercalcemia and hypophosphatemia were found more or less by accident. In this case careful observation over a period of two years failed to disclose any symptoms which could be referred to hyperparathyroidism; yet exploration disclosed a parathyroid tumor. It is evident, therefore, that hyperparathyroidism may occur without conspicuous osseous disease and without renal calculi. In the case being reported, the roentgenographic changes in the skeleton were minimal and not in themselves pathognomonic of hyperparathyroidism, although they become highly significant when viewed in the light of the postmortem observations.

When hyperparathyroidism occurs without either skeletal or renal involvement, the only symptoms that one might expect to encounter would be those resulting from hypercalcemia per se or from the resulting hypercalciuria. These include nausea, vomiting, anorexia, loss of weight, epigastric pain, weakness, constipation, polyuria and polydipsia. Hypervitaminosis D results in hypercalcemia and may also produce such symptoms. Hypervitaminosis D may also result in renal insufficiency or the formation of renal stones. It must, therefore, be carefully excluded before a diagnosis of hyperparathyroidism is made.

Renal Insufficiency.—Death in this case was probably the result of renal insufficiency secondary to hyperparathyroidism. The kidneys showed atrophy, in contrast to the 2 cases of hyperparathyroidism previously reported, in which hypertrophy of the kidneys was present. However, in this instance hyperparathyroidism may have existed for a longer period, and it is possible that the changes observed in these kidneys represent a later stage of the disease. Evidence of changes resulting from hyperparathyroidism is superimposed on the changes that are manifestations of vascular disease of the kidneys in this case. The calcium content of the kidneys was fifty to seventy-five times that found in normal kidneys.

Although the patient had evidence of considerable arterial disease of the kidneys, the degree of destruction of nephrons and replacement by fibrous tissue was out of all proportion to the degree of arterial

6. Albright, F.; Sulkowitch, H. W., and Bloomberg, E.: Further Experience in the Diagnosis of Hyperparathyroidism, Including a Discussion of Cases with a Minimal Degree of Hyperparathyroidism, Am. J. M. Sc. **193**:800-812 (June) 1937.

7. Keating, F. R., Jr.: Unpublished data.

disease. In our experience, death from renal insufficiency as the result of senile arteriosclerosis of the kidneys alone is rare. Also a significant degree of azotemia in an elderly patient can rarely be ascribed to senile renal arteriosclerosis alone and without accompanying hypertension, chronic pyelonephritis or obstructive lesions of the urinary tract.

Gastrointestinal Features.—The gastrointestinal manifestations of hyperparathyroidism deserve further emphasis. Gutman and his associates [8] in 1934 described anorexia, nausea, vomiting, constipation and epigastric pain in cases of hyperparathyroidism and stated that these symptoms may so dominate the picture as to suggest that they are due to duodenal ulcer or appendicitis. It is a common fallacy to attribute symptoms of abdominal pain and vomiting first to some intra-abdominal disease and to assign a secondary etiologic role to a systemic disease which may chance to coexist. Because of this, it is not surprising that if an intra-abdominal lesion is found which could explain such symptoms the possibility that they result from an associated systemic disease is not seriously considered.

Vomiting is a common symptom of gastrointestinal disease. Peptic ulcer involving either the stomach or the duodenum is frequently accompanied with this symptom, but when vomiting is severe it is usually because the ulcer has been complicated by pyloric obstruction as a result either of spasm or of cicatricial change. In uncomplicated duodenal ulcer, involuntary vomiting, as distinguished from regurgitation and voluntary vomiting, is uncommon. Nervous and hysterical patients who have duodenal ulcer without any associated obstructive complication may have definite symptoms of nausea and vomiting. There are certain cases of duodenal ulcer in which there is no manifestation of the activity of the disease, except for severe unheralded and often protracted episodes of vomiting; this has been called the crisis type of duodenal ulcer.

If a patient who has duodenal ulcer has vomiting as a prominent symptom and it can be determined that the vomiting is not due to some complication of the duodenal ulcer or a functional manifestation, the explanation for the vomiting should be sought in some other disease process if adequate treatment of the ulcer fails to control the symptoms.

The lack of control of symptoms in this case was attributed to intractability on the part of the ulcer, and the possible significance of moderate aggravation of symptoms following treatment, considered adequate, was not recognized. When the history and course are reviewed in the light of the postmortem findings, they may be interpreted in a far different light than that which appeared most reasonable at the

8. Gutman, A. B.; Swenson, P. C., and Parsons, W. B.: The Differential Diagnosis of Hyperparathyroidism, J. A. M. A. **103**:87-94 (July 14) 1934.

time of observation. On the basis of our retrospective knowledge that the duodenal ulcer was healed, it appears likely that the gastric symptoms which were present during the last eleven months of life were entirely manifestations of hyperparathyroidism. Treatment for the supposedly active ulcer not only failed to bring relief but can safely be presumed to have accelerated the injurious effect of the hyperparathyroidism on the kidneys and also, perhaps, on the blood vessels. The patient was probably correct in stating, as he did, that milk did not agree with him.

Albright has pointed out that demonstrable disease of bone does not develop in cases of hyperparathyroidism if a positive calcium balance is maintained. The fact that the usual diet taken by patients with ulcers is high in calcium and that this patient had symptoms of ulcer intermittently over a period of twenty-six years suggests that he probably maintained an intake of calcium higher than normal for many years. He should have been able to maintain calcium balance fairly well despite the association of hyperparathyroidism, but the finding of osteitis fibrosa cystica at necropsy shows that this was not the case.

Albright also suggested that if the serum calcium content is near the critical level a slight increase of it may precipitate symptoms of parathyroid poisoning and that a diet high in calcium or phosphorus may suffice to elevate the serum calcium content above the critical level. He emphasized that a patient who has severe hyperparathyroidism should be kept on a low intake of calcium and phosphorus until there is no longer any danger of parathyroid poisoning. Milk, which is the sheet anchor of the dietary for patients with ulcer, has, therefore, no place in the dietary program of the patient who has hyperparathyroidism. According to Sherman,[9] the average daily requirement of men is 0.68 Gm. of calcium and 1.32 Gm. of phosphorus. The average diet for patients with ulcer contains from 1.7 to 1.8 Gm. of calcium and from 1.3 to 1.4 Gm. of phosphorus daily. Such a high intake of calcium and phosphorus could probably precipitate acute parathyroid poisoning in cases of hyperparathyroidism. Such a sequence of events was apparently operative in 2 similar cases reported elsewhere by one of us (Rogers).

The fact that this case represents the third instance in which the association of probable hyperparathyroidism and peptic ulcer was observed at necropsy during one year at the Mayo Clinic suggests that this association may not be a chance one. There seems no compelling reason to suppose that hyperparathyroidism would favor the production of peptic ulcer, and chronologically it looks as if ulcer may

9. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 6, New York, The Macmillan Company, 1941.

have preceded parathyroid disease in this case. One may, therefore, wonder if treatment for ulcer over a long period may not have stimulated parathyroid hyperfunction as a result of the excess ingestion of alkalis, of calcium or of phosphorus.

The decided calcification of the pancreas is of considerable interest. Just what role the hyperparathyroidism played in the production of the pancreatic lithiasis is problematic. Although the pancreatic lithiasis may have been entirely secondary to recurrent pancreatitis, there was no past history for this, and it is possible that the tendency toward calcification elsewhere in the body, attributable to the hypercalcemia of hyperparathyroidism, may have played a part in the production of the pancreatic lithiasis. From the evidence at hand, one cannot say whether this is the case or whether the extensive pancreatic calcification was merely incidental.

SUMMARY

A case is reported in which pronounced clear cell hyperplasia of the parathyroid glands and primary hyperparathyroidism were associated with healed duodenal ulcer. The parathyroid glands weighed 47.56 Gm. Peripheral gangrene developed as a terminal event. Death resulted from renal insufficiency secondary to nephrocalcinosis. Pancreatic lithiasis and mild osteitis fibrosa cystica were also disclosed at necropsy. An unusual type of necrosis of arterial walls, with intimal calcification, appeared responsible for the gangrene of the peripheral parts. Gastrointestinal symptoms, which were presumed during life to be due entirely to ulcer, appeared in retrospect to have been manifestations of severe hyperparathyroidism.

COINCIDENCE OF DIABETES MELLITUS AND HYPOPITUITARISM

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THE INFLUENCE of the endocrine glands other than the pancreas on diabetes has been studied extensively. While the pancreas has always been the focus of research efforts, the modifying effects of other endocrine glands, notably the thyroid and adrenal glands, have also been considered of great importance. The research of Houssay and his associates [1] and of many other workers during the past fifteen years on the interrelationships of the pituitary, adrenal and pancreas is well known. The disease diabetes mellitus responds sensitively, either for better or for worse, to changes in the pituitary and adrenal. These changes may be artificially produced either by operation on the two glands or by injection of their hormones. The classic animal with the Houssay phenomenon is one in which diabetes has been produced by pancreatectomy and subsequently alleviated by hypophysectomy. An almost identical phenomenon can be produced by bilateral adrenalectomy only when the salt level is maintained.

The human equivalents of animals with the Houssay phenomenon are rare indeed. Reports of cases in which diabetes mellitus has been mitigated by the subsequent declining function of the adrenal or pituitary are exceptional. Some 16 cases of coincidence of diabetes and Addison's disease have been reported. Of these, only 4 apparently showed decreasing requirements for insulin as the hypoadrenalism developed.

The coincidence of diabetes mellitus and hypopituitarism is rarer still. We have found reports of only 3 patients displaying this phase of the Houssay phenomenon. In this paper we are reporting a fourth case.

1. Houssay, B. A.; Foglia, V. G.; Smith, F. S.; Rielti, C. T., and Houssay, A. B.: The Hypothesis and Secretion of Insulin, J. Exper. Med. 75:547-566, 1942.

REPORT OF A CASE

A 50 year old white married woman was admitted to Albany Hospital on July 2, 1943. Her chief complaints were headache, vomiting, dizziness, diarrhea and fainting spells.

The patient was in good health until thirty-one years ago. At that time she had a thyroidectomy, with apparent relief from the symptoms of hyperthyroidism. Subsequently she had an operation for the removal of fibroid tumors from the uterus and an operation on the breast the nature of which is not known.

Twelve years ago the patient's symptoms were diagnosed as diabetes mellitus, and she was treated in Detroit, where she received 50 units of insulin for ten days and then took 35 units of insulin a day for five to six months. From 1931 to 1934 she took 20 units of insulin a day sporadically but followed no strict regimen. For two or three years before her admission to the hospital she did not take any insulin at all. However, urinalyses often revealed sugar until about one year before admission, when the specimens of urine were consistently negative for sugar.

The patient was otherwise well until May 1, 1943, when she complained of a severe headache over her left eye. She became weak and started vomiting. For this she was hospitalized elsewhere for two weeks and then discharged as improved, without a diagnosis being made. One week after discharge, severe headaches returned and the patient's sense of smell seemed to be extremely acute. She was nauseated at the sight of food and would often vomit, sometimes without apparent cause. The vomitus was described as somewhat projectile in nature. When she stood, she became dizzy and weak. Her appetite became poor, and she began to lose weight. On several occasions when getting out of bed to go to the bathroom, she fell to the floor and lost consciousness temporarily. At these times, her hands assumed a clawlike position and she lost control of both her anal and her bladder sphincters. After these spells, the patient was weak and sweated excessively.

On June 1, 1943, the day before her admission to the hospital, the patient began to act rather silly for about two hours in the morning. She made faces at her husband, played peek-a-boo with the bed clothes and talked incoherently. After this, she appeared normal and slept. The next morning she was restless and thrashed her arms and legs about the bed. She talked only in a whisper and occasionally screamed in a loud voice. She was unable to retain food or fluids. Later in the day she began whispering and screaming and complained of a headache. She was brought to the hospital.

Family History.—One brother had diabetes, and the patient's mother died of diabetes. Her father died of carcinoma of the liver; the primary site was not known.

Past History.—The patient was married twenty-six years. She had always been pampered by her husband, who appeared to be a reliable and intelligent man. She reacted excessively to minor misfortunes, smoked excessively and drove an automobile extremely conservatively, i. e., 10 miles an hour.

Physical Examination.—The temperature was 99.2 F., the pulse rate 92, the respiratory rate 24 and the blood pressure 75 systolic and 30 diastolic. The abnormal findings were limited to the skin, which showed slight scleroderma, a thyroidectomy scar, a scar beneath the left breast and a laparotomy scar in the midline; the heart and lungs were essentially normal.

Neurologic Examination.—The left pupil was irregular and small but reacted to light. The right pupil was small and regular, reacting to light sluggishly.

There was variable spasticity of the arms and legs. Questionable deep reflexes were elicited from the left leg. The right leg and upper extremities showed normal reflexes. The abdominal reflexes were absent. The finger to nose test showed a 2 to 3 cm. deviation on the left.

Mental Status.—The patient's mood was one of flatness and indifference. She answered questions slowly and was able to give a chronologic account of her illness. She seemed oriented in all spheres when she was first seen.

Laboratory Data.—The urine showed a trace of albumin. The blood showed a hemoglobin content of 89 per cent; a red blood cell count of 4,900,000, with a color index of 0.96; a white blood cell count of 8,200, with a differential count of lymphocytes 73 per cent and polymorphonuclear leukocytes 27 per cent, and a hematocrit reading of 42 per cent. Wassermann tests of the blood and spinal fluid elicited negative reactions. The protein content was 44.2 mg. per hundred cubic centimeters, sugar content 35 mg., chloride contents 680 mg. and initial pressure 140 mm. of water. Roentgenograms, including a series of the gastrointestinal tract, were normal except for calcified mesenteric nodes. There was increased density of the left side of the pelvis, with no evidence of metastatic tumor in the lungs or in the ribs; the skull was normal. The basal metabolic rate was + 12 per cent. The blood sugar content was 61 mg. per hundred cubic centimeters. Gastric analysis showed 10 degrees of free hydrochloric acid.

Course in Hospital.—Because of the low initial blood pressure, this determination was repeated and showed, with the patient lying down, a pulse rate of 72 and a blood pressure of 75 systolic and 30 diastolic. With the patient sitting up, the pulse rate was not detectable and the blood pressure was 30 systolic and 0 diastolic. A tentative diagnosis of Addison's disease was made, and a determination of blood sodium content at this time showed the sodium content to be 327 mg. per hundred milliliters of serum. This was within normal range.

The patient became clear mentally and was in good contact. She became weak on sitting, somewhat faint and dizzy and required support. On July 15, 1943 she vomited twice and noted headache when she lay back. She was given isotonic solution of sodium chloride and dextrose intravenously and vitamins. She complained of pain in the knees; her knees on admission had been stiff and showed increasing lack of mobility as her stay in the hospital progressed. Her knees were painful on both active and passive motion. No pigmentation was noted. On a high sodium, low potassium diet, the patient showed no significant improvement. The provocative sodium withdrawal test was not attempted. Medical consultation was obtained, and the observations listed heretofore were corroborated. The suggestion was made that perhaps hypoactivity of the pituitary and thyroid might be indicated here. Studies of the blood pressure, which were made on the twenty-fifth day in the hospital, showed an initial blood pressure of 110 systolic and 60 diastolic with the patient horizontal and a drop to 72 systolic and 50 diastolic as the patient was gradually elevated. With the patient lying at an angle of 90 degrees, with the legs dependent, the blood pressure was 60 systolic and 40 diastolic. After an intramuscular injection of 0.5 cc. of epinephrine, with the patient at an angle of 90 degrees, with the legs dependent, there was no essential change in the blood pressure and she became nauseated. With the patient at an angle of 70 degrees and the legs elevated the blood pressure rose as high as 164 systolic and 82 diastolic, and with the patient lying flat the blood pressure was 130 systolic and 70 diastolic with the use of epinephrine.

On July 30, 1943, administration of adrenal cortical extract was started. Five cubic centimeters was given daily by intramuscular injection. On the first day

the blood pressure was 118 systolic and 66 diastolic with the patient reclining and 60 systolic and 44 diastolic with the patient sitting. On several occasions the blood pressure rose to 120 systolic and 70 diastolic, but there was no other essential change in the patient's condition. On Aug. 4, 1943 the patient became semicomatose, lashed around in bed, was unable to talk and vomited several times. Her muscles were spastic, and her hands were held in a clawlike position. Trousseau's sign was positive; there was no Chvostek's sign. Thereupon calcium gluconate was administered, with slight response. The patient was treated intravenously with a solution of dextrose in isotonic solution of sodium chloride, with some improvement, although she was not fully conscious all the time. Her speech was thick and she continued to vomit. On Aug. 6, 1943 the patient's blood pressure when reclining was 112 systolic and 65 diastolic, this being the seventh day of treatment with desoxycorticosterone acetate. She was fully conscious but was still weak and unable to retain food and was sustained on dextrose in isotonic solution of sodium chloride given intravenously. On the ninth day of this treatment the patient felt much better. Medication was supplemented by 30 drops of viosterol a day. On August 10 she became comatose and did not respond. However, she became conscious after 50 cc. of .50 per cent dextrose was given. Determination of blood sugar content taken the next morning with the patient in a fasting condition showed 35 mg. per hundred cubic centimeters. Thereupon the patient was maintained on dextrose given intravenously until her fasting sugar content rose to 122 mg. per hundred cubic centimeters, on August 14. Fluids high in sodium were also given.

By August 19 her blood pressure was 100 systolic and 70 diastolic, and therapy with adrenal cortical extract, which had been temporarily discontinued, was resumed. The patient felt much improved for several days. On August 23 there was another hypoglycemic reaction, which was relieved by administration of 25 per cent dextrose and 5 per cent dextrose in isotonic solution of sodium chloride. The dosage of desoxycorticosterone acetate was reduced to 0.5 cc. per day. Determination of blood sugar content taken at the time of this episode was 45 mg. per hundred cubic centimeters. On August 24 use of desoxycorticosterone acetate was discontinued. On August 26 there was another hypoglycemic reaction. The patient was unconscious and spastic, but she responded a half-hour after infusion of dextrose was begun. Use of desoxycorticosterone acetate was again resumed. These episodes of hypoglycemia recurred again despite intensive intravenous administration of dextrose in isotonic solution of sodium chloride. The patient was still unable to take solid food by mouth. At these times the blood sugar content was about 43 mg. per hundred cubic centimeters. On September 2 she was again unconscious, and 125 Gm. of sugar plus isotonic solution of sodium chloride was given without the patient's becoming conscious again. The blood sugar content at this time was 57 mg. per hundred cubic centimeters. An attempt was made to carry her along on dextrose and isotonic solution of sodium chloride, but she never fully regained consciousness, although there was one day when she appeared to recognize things about her. The patient went downhill, dying on Sept. 14, 1943.

The cardinal clinical symptoms of Simmond's disease were not noted in our patient except to the following limited extent. Cachexia or emaciation was not decided. The patient had lost weight but was not seriously emaciated. The atrophy of the buttocks, which has been

reported as striking in several cases (Escamilla and Lisser, 1942[2]), was not decided. Premature aging was not prominent. The patient was 50 years but appeared about 55 or 60. Axillary and pubic hair was present but less abundant than normally. Genital atrophy or infantilism was not apparent. The blood pressure is frequently affected in Simmond's disease. Some patients have had mild hypertension, but others have suffered from severe hypotension, almost as low as that in Addison's disease. Postural hypotension has been stressed by one worker (Schellong, 1930, 1931, 1932). Our patient's most salient symptom was the extreme postural hypotension, so severe that on several occasions she lost consciousness when elevated from the reclining to the setting position. An extremely low basal metabolic rate characterizes Simmond's disease. Our patient's rate was $+12.5$ per cent. The fasting sugar content has been reported as 60 mg. per hundred cubic centimeters or below in about 20 per cent of all cases. The fasting blood sugar content of our patient on several occasions was as low as 35, 43, 45 and 57 mg.

Postmortem Observations.—At autopsy, pathologic changes were found in the pancreas, adrenals and pituitary, by far the most striking changes being observed in the pituitary, which showed notable degenerative changes. The adrenals were smaller than normal; the cortices were narrowed and bore small deposits of hyaline material. The changes in the adrenals, however, were judged insufficient to account for clinical adrenal insufficiency. A detailed pathologic report is appended.

<div style="text-align:center">COMMENT</div>

The patient here reported was a 50 year old woman with diabetes mellitus in whom the pancreas, thyroid, adrenal cortex and pituitary glands seem to have deviated from normal, to a greater or less degree. At the age of 19 she required a thyroidectomy for hyperthyroidism. At 38 she was found to be diabetic and required insulin in dosages as high as 35 to 50 units daily for a period. Three months before her death a hypopituitary-hypoadrenal syndrome, including hypoglycemic crises, developed. At autopsy, the pituitary gland was found to be almost completely destroyed, with secondary changes in the adrenal cortices.

The influence of her hyperthyroidism on the diabetes, which developed two decades later, is dubious, but the presence of the condition does reflect a dysbalanced endocrine organization of the body. Of cardinal interest in this case is the endocrine alteration which occurred later in her life. the mitigation of the diabetes mellitus by a condition clinically

2. Escamilla, R. F., and Lisser, H.: Simmond's Disease: Clinical Study with Review of Literature; Differentiation from Anorexia Nervosa by Statistical Analysis of 595 Cases, 101 Proved Pathological, J. Clin. Endocrinol. 28:171-178, 1942.

resembling hypoadrenalism and pathologically falling best into the category of hypopituitarism with secondary hypoadrenalism.

With regard to the use of the word "coincidence," it should be explained that complete chronologic concurrence is not implied but rather the coexistence of the two diseases in the same patient at different periods. The diabetes is proved to have existed about three years before the appearance of the adrenocortical insufficiency and that of the anterior lobe of the pituitary. It was felt possible to assume that the gradual improvement in the diabetes, a disease with rare remissions, was due to the progressive development of the pituitary-adrenal syndrome.

THE PITUITARY AND DIABETES MELLITUS

The antagonism between the pituitary and the pancreas is one aspect of the complex relationship between them. The research of Houssay and his co-workers became the nucleus of all the experimental and clinical data now throwing light on this phase of carbohydrate metabolism.

Houssay and his co-workers in 1942 reviewed all the previous work on the pituitary carbohydrate relationship. The actions of the pituitary may be summarized as follows: 1. Hypophysectomy reduces the intensity of pancreatic and phlorhizin diabetes. 2. Hypophysectomy produces sensibility to the hypoglycemic action of insulin (and also to other hypoglycemic agents, including phlorhizin and fasting). 3. Anterior pituitary extract produces effects which are the opposite of the two previously noted. It increases resistance to hypoglycemic agents, and it aggravates diabetes. If the diabetes is the severe type resulting from complete pancreatectomy, it is intensified. If it is the milder diabetes found in dogs with both pancreas and pituitary removed, it is made much worse. In normal dogs, pituitary extract can produce diabetes. 4. Overactivity of the pituitary causes glycosuria evident in about one third of acromegalic cases. Some acromegalic patients, moreover, show increased resistance to insulin. 5. The pancreas after hypophysectomy has been shown to contain increased islet tissue in some animals. 6. Injections of pituitary extracts into animals produce varying effects on the pancreas. These are discussed in detail by Houssay.

The Houssay phenomenon refers to the disappearance of diabetes by means of hypophysectomy. Hypoglycemic crises occur frequently in animals with the Houssay phenomenon and can be prevented by injection of anterior pituitary extract.

We have been able to find 3 other cases in the literature in which the Houssay phenomenon has been spontaneously duplicated in human beings. In 1932 Calder[3] briefly mentioned a patient with Simmond's disease who before treatment had a type of sugar tolerance curve "characteristic

3. Calder, R. M.: Anterior Pituitary Insufficiency (Simmond's Disease), Bull. Johns Hopkins Hosp. **50**:87-114, 1932.

of a mild diabetes," on two occasions showing slight glycosuria. After treatment for the pituitary dysfunction "the sugar tolerance curve became normal and glycosuria disappeared."

Lyall and Innes,[4] in 1935, described a case of severe diabetes in a man aged 29 in whom much improvement in the diabetes became evident concurrently with the development of a pituitary lesion. His diabetes first manifested itself at 27 years, requiring 80 units of insulin daily. The insulin requirements, however, gradually declined. Six months later sugar tolerance tests showed diminished severity of the diabetes, and it was thought possible that an insulogenic adenoma of the pancreas was developing. Roentgenograms of the skull, however, showed a definite evidence of a pituitary tumor, "an abnormally dense deposit lying under the sella." A neurologic examination was noncontributory. When discharged from the hospital the patient remained sugar free and well without insulin. The nature of the pituitary lesion was still doubtful at the time of the authors' report, but they felt that it might be classified as a cystic adenoma which was becoming calcified or a meningioma arising from the dorsum sellae. This condition did not progress to spontaneous hypoglycemia.

A third instance of the Houssay phenomenon was reported by Kotte and Vonderahe [5] in 1940, that of a 40 year old man with diabetes mellitus of five years' duration who died of acute hypoglycemia. The diabetes had been diagnosed in an Irish hospital, had been treated by irregular administration of insulin "as the need arose" and was apparently of relatively mild severity. The patient was well until two months before his admission to the hospital, when loss of weight, easy fatigability and other symptoms developed, but he continued to work. Three days before his admission to the hospital a physician found that the urine contained "an excessive amount of sugar." He entered the hospital with "pallor, sweating, urinary incontinence and such excessive weakness that he could not talk above a whisper." He died eighteen hours after admission, having remained in a semistuporous state throughout hospitalization. Blood sugar levels, returned after death, were read at 31 and 20 mg. per hundred cubic centimeters.

The observations at autopsy revealed massive infarction with necrosis of the anterior pituitary, reported as "an area of partially disintegrated, pale staining cells implicating the entire anterior lobe except for a few normal glandular cells along some portion of the periphery." The pancreas and adrenals were normal both grossly and microscopically.

4. Lyall, A., and Innes, J. A.: Diabetes Mellitus and the Pituitary Gland: A Case of Diabetes with Intercurrent Pituitary Lesion and Concomitant Improvement of Diabetes, Lancet **1**:318-321, 1935.

5. Kotte, J. H., and Vonderahe, A. R.: The Houssay Phenomenon in Man: Report of Case of Diabetes Mellitus, Infarct of Anterior Lobe of Pituitary Body and Terminal Hypoglycemia, J. A. M. A. **114**:950-953 (March 16) 1940.

These are the only cases recorded of spontaneous development of the Houssay phenomenon in human beings. Some workers, however, have attempted to alleviate diabetes mellitus by roentgen therapy or surgical treatment directed at the pituitary. Since hypophysectomy reduces the severity of experimental diabetes, attempts have been made to produce similar results by means of heavy doses of roentgen rays. Cushing [6] (1932) successfully treated in this way a patient with pituitary basophilism showing hyperglycemia. This patient required 65 units of insulin daily, but after irradiation he became entirely sugar free on an ordinary diet without insulin.

Hutton [7] (1933, 1937 and 1939) has stated that he has successfully treated diabetes by irradiation of the hypophysis. In a series of about 50 patients he stated that "one third experienced no improvement of any kind; one third experienced symptomatic improvement, such as a decrease in headache, mental depression, nervousness and pains in the extremities, without any noteworthy change in the carbohydrate tolerance, and one third showed considerable improvement in carbohydrate tolerance, some being able, after treatment, to get along without insulin." No detailed data for these patients were given. This work is considered "unconvincing and inconclusive" (Rynearson and Hildebrand, 1941 [8]). Dobrin and Lucinian in 1935 [9] reported the trial of this technic in 3 children aged 12 to 16, without lasting benefit. Selle, Westra and Johnson [10] were unable to confirm the favorable results of irradiation in their studies of 7 diabetic (depancreatized) dogs.

Surgical ablation of the anterior lobe of the pituitary was attempted by Chabanier in 1936 [11] in a case of severe diabetes. Prior to operation the patient required from 150 to 170 units of insulin daily, the blood

6. Cushing, H.: Papers Relating to the Pituitary Body: Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C Thomas, Publisher, 1932.

7. Hutton, J. H.: Irradiation of the Pituitary and Adrenal Glands in Essential Hypertension and Diabetes, Clin. Med. Surg. **44**:533-536, 1937; Roentgenotherapy of Endocrinopathies, Arch. Phys. Therapy **20**:287-293, 1939; Diabetes Mellitus and Essential Hypertension: Theory as to Their Etiology and Treatment, Illinois M. J. **64**:539-547, 1933.

8. Rynearson, E. H., and Hildebrand, A. G.: Metabolism and Diabetes: Review of Certain Recent Contributions, Arch. Int. Med. **68**:134-175 (July) 1941.

9. Dobrin, M., and Lucinian, H. H.: Diabetes Treated by Irradiation of Hypophyses, J. Florida M. A. **21**:550-551, 1935.

10. Selle, W. A.; Westra, J. J., and Johnson, J. B.: Attempts to Reduce the Symptoms of Experimental Diabetes by Irradiation of the Hypophysis, Endocrinology **19**:97-104, 1935.

11. Chabanier, H.; Puech, P.; Lobo-Onell, C., and Lelu, E.: Hypophyse et diabete (a propos de l'ablation d'une hypophyse normale dans une cas de diabete grave), Presse méd. **44**:986-989, 1936.

sugar content averaging 400 mg. per hundred cubic centimeters. After operation the blood sugar level ranged from 75 to 220 mg. per hundred cubic centimeters and the diabetes seemed improved, but the patient died five months postoperatively of pulmonary tuberculosis. The condition did not progress to spontaneous hypoglycemia.

An exhaustive review of the literature of Simmond's disease by Escamilla and Lisser [2] (1942) included an evaluation of sensitivity to insulin and of frequency of hypoglycemic coma. Among the 101 pathologically verified cases of Simmond's disease—all that could be found in the literature—hypoglycemic coma occurred in only 5. In 338 suggestive or typical clinical cases of Simmond's disease lacking pathologic investigation on the whole, only 1 case with episodes of hypoglycemic coma occurred. Frank diabetes mellitus has been reported in only 1 case of verified Simmond's disease, according to Escamilla and Lisser. No statement is made as to the alleviation of the diabetes by the hypopituitarism in this case.

THE ADRENALS AND DIABETES MELLITUS

The severity of diabetes in depancreatized animals can be alleviated not only by hypophysectomy (Houssay) but also by bilateral adrenalectomy. Another phenomenon analogous to that associated with the pituitary is found in the fact that injections of large quantities of adrenal cortical extract into adrenalectomized depancreatized animals increases the severity of diabetes (Joslin, 1940 [12]). Long and his co-workers have reported this work in a series of papers since 1934. They feel that hypophysectomy relieves diabetes by causing hypoadrenalism. This explanation is considered not completely tenable. Recent work by Long [13] (1940) suggests that not all the pituitary effect is so mediated but that the two hormones work synergistically.

Joslin (1940) pointed out that epinephrine exerts a significant effect on carbohydrate metabolism but an effect of only transient nature, "not fundamental in the sense that the anterior pituitary hormone is." Epinephrine increases glycogenolysis of the liver, thus opposing the formation of glycogen by insulin. The result is a rise in blood sugar content.

Injection of epinephrine by itself does not produce diabetes. There is, therefore, no condition analogous to pituitary diabetes. Moreover, the removal of the adrenal medulla does not improve the diabetes of depancreatized animals.

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12. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1940.

13. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309-344, 1940.

Denervation of the adrenals, celiac ganglionectomy or splanchnic nerve section have been found by deTakats and Cuthbert [14] (1932) to increase sensitivity to insulin in animals. Of 2 patients on whom bilateral splanchnic nerve section was carried out, 1 showed some improvement whereas the other was not benefited. Rogoff [15] (1936) reported a patient who underwent this operation, was not relieved of the diabetes and died in about a year of Addison's disease. The patient here reported clinically resembled a person with Addison's disease and at autopsy showed slight to moderate destructive changes in the adrenal. A brief survey of patients showing coincidence of diabetes and Addison's disease has been made, and 16 such patients have been found. The first well documented summary was reported by Arnett in 1927,[16] but Unverricht had mentioned a patient the year before. Arnett also reviewed five previous instances, all of which he considered questionable. Two patients were mentioned in a brief note from the Mayo Clinic (1930). Since 1930, instances of this association have been noted by Gowen [17] (1932), Simpson (1932), Crooke and Russell [18] (1935), Bloomfield [19] (1939), Rhind and Wilson [20] (1941) and McCullaugh [21] (1942). The unique case of Addison's disease produced by adrenal denervation reported by Rogoff in 1936 has been noted previously. Of these 16 cases, only 4 showed a decreased need of insulin because of the subsequently developing Addison's disease. Bloomfield's patient required only 4 to 6 units of insulin, although the original requirement was 40 units. McCullaugh's patient apparently displayed an almost full remission of diabetes.

SUMMARY

A patient with diabetes mellitus associated with hypopituitarism is reported. The patient's diabetes gradually improved as the hypopituitarism became severer, and she died after a prolonged course in the

14. deTakats, G., and Cuthbert, F. P.: Effect of Celiac Ganglionectomy on Sugar Tolerance of Dogs, Am. J. Physiol. **102**:614-619, 1932.

15. Rogoff, J. M.: Addison's Disease Following Adrenal Denervation in Case of Diabetes Mellitus, J. A. M. A. **106**:279-281 (Jan. 25) 1936.

16. Arnett, J. H.: Addison's Disease and Diabetes Mellitus Occurring Simultaneously, Arch. Int. Med. **39**:698-704 (May) 1927.

17. Gowen, W. M.: Addison's Disease with Diabetes Mellitus, New England J. Med. **207**:577-579, 1932.

18. Crooke, A. C., and Russell, D. S.: Pituitary Gland in Addison's Disease, J. Path. & Bact. **40**:255-283, 1935.

19. Bloomfield, A. L.: Coincidence of Diabetes Mellitus and Addison's Disease: Effect of Cortical Extract on Glycemia and Glycosuria, Bull. Johns Hopkins Hosp. **65**:456-465, 1939.

20. Rhind, E. G. G., and Wilson, A.: Diabetes Mellitus in Addison's Disease, Lancet **2**:37-38, 1941.

21. McCullagh, E. P.: Two Cases of Diabetes Mellitus, One with Myxedema, and One with Addison's Disease, Cleveland Clin. Quart. **9**:123-134, 1942.

hospital marked by several hypoglycemic episodes. The relationship among the pituitary, adrenal cortex and pancreas has been reviewed, with special reference to the so-called Houssay phenomenon. This is apparently the fourth recorded case representing this phenomenon.

DETAILED PATHOLOGIC REPORT

The body of this patient, examined one hour and twenty-five minutes after death, was that of a somewhat undernourished 50 year old woman whose cutaneous surfaces were pale. Superficially no significant pathologic changes were observed. The heart likewise showed nothing of note, but patchy acute bronchopneumonia was present in the lungs. The pancreas appeared smaller than normal, had a dull grayish white color and was softer than usual. On section the pancreatic lobules were indistinct. Histologically, the striking observation in the pancreas was the presence of decided sclerosis of both arteries and arterioles. Large foci of interstitial fibrosis were present. In these scars the acinar tissue was missing, but islets of Langerhans still remained. Small numbers of islets contained minute accumulations of hyaline material, which was present between the islet cells.

The adrenal glands were smaller than normal, and on section the cortical portions appeared thin and had a dull white color. The medullary portions were not remarkable. Histologically, decided arterial and arteriolar sclerosis was again evident. There were many extracapsular masses of cortical tissue, in some of which a hyaline material replaced the cells in the central portions. The capsules of the glands themselves were thickened, and the cortices were narrowed. Deep in the cortices were the same small deposits of hyaline material which were seen in the extracapsular cortical tissue. Histologically, neither gland presented enough destruction of the cortical cells to account for clinical adrenal insufficiency.

The pituitary gland, however, showed notable changes. Grossly it was larger than normal, and in the tissues of the anterior lobe focal hemorrhages were noted. Microscopically decided degenerative changes were found. There was a large zone of hyaline necrosis in the anterior lobe. In it were large numbers of cholesterol crystal clefts, many of which were surrounded by foreign body giant cells. Approximately four fifths of the anterior lobe appeared to be destroyed. In appearance the necrosis strongly resembled that found in large atheromas, such as sometimes occur in the aorta. About the periphery of this focus of necrosis were small numbers of anterior lobe cells whose outlines were indistinct and whose cytoplasm was vacuolated. Focal hemorrhages were present, and numbers of hemosiderin-filled macrophages were scattered throughout the viable portions of the anterior lobe. Small collections of lymphocytes and plasma cells were also noted near the junction of the anterior and posterior lobes.

PENICILLIN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

A Study of the End Results in Thirty-Four Cases, with Particular Reference to Dosage, Methods of Administration, Criteria for Judging Adequacy of Treatment and Probable Reasons for Failures

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THE STUDIES concerned in this report were begun in July 1943 because of the belief that the previous failure of subacute bacterial endocarditis to respond to penicillin might be due to inadequate dosage and too short a period of treatment for a disease of this character.

To date 38 patients have been treated or are under treatment. The first 34 were selected for this report because the "recoveries" have been observed long enough for us to be reasonably sure of permanency in view of our accumulated experience. Relevant data on the first 20 cases are presented in the accompanying tables (tables 1 and 2). The first 4 cases of recovery (cases 3, 4, 5 and 8) were reported in June 1944.[1]

METHOD OF STUDY

Attempt was made to establish the approximate date of onset of the disease and the immediately predisposing illness such as infection of the upper respiratory tract, "influenza" or extraction of teeth. No patient was included in the study unless cultures of the blood yielded pathogens, even though clinical findings made the diagnosis likely. Laboratory examinations on the patients' admission

1. (a) Priest, W. S., in discussion on Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Discussion on Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with Analysis of One Hundred and Fifty Cases in Which It Was Employed, J. A. M. A. **125**:1003 (Aug. 12) 1944. (b) Priest, W. S., and Smith, J. M.: Penicillin in the Treatment of Subacute Bacterial Endocarditis, Proc. Inst. Med. Chicago **15**:256 (Feb. 15) 1945.

to the hospital consisted in complete blood cell count; urinalysis; culture of urine; Kahn test; determination of the sedimentation rate, blood nonprotein nitrogen and chloride levels, carbon dioxide–combining power, total protein content and albumin-globulin ratio; tests of renal function; sulfobromophthalein test of hepatic function;

TABLE 1.—

Case	Sex	Age, Yr.	Duration of Disease, Wk.*	Organism	Sensitivity to Penicillin, Units/Cc.	Daily Dose of Penicillin	Number of Days on Each Dose	Anticoagulants	Number of Courses of Penicillin †	Total Days on Penicillin
3	F	24	20	Str. viridans	0.06	200,000 200,000 200,000 450,000	(29) (20) (9) (22)	Heparin Heparin Heparin	3	80 .. ..
4	M	34	7	Str. haemolyticus	0.04	200,000	(27)	Heparin	1	28
5	M	21	15	Str. viridans	0.10	100,000 200,000 200,000	(3) (24) (16)	Heparin Heparin Heparin	2	44
8	F	44	16	Str. viridans	0.04	200,000 400,000	(14) (15)	Heparin Dicumarol	1	..
			8 ††	.... Str. viridans	.... 0.04	.... 200,000 400,000	.... (9) (29)	.... Heparin Dicumarol	1	67
10	F	32	12§§	Str. viridans	0.06	200,000 400,000	(28) (28)	Dicumarol Dicumarol	.. 2	.. 56
11	M	74	10§§	Str. viridans	0.06	300,000 400,000	(28) (25)	.... No anticoagulant	.. 2	.. 53
14	F	14	5½	Str. viridans	?	200,000 400,000	(16) (29)	.... No anticoagulant	.. 2	.. 48
15	F	29	24	Str. viridans	0.02 0.02	100,000 to 150,000 150,000 to 400,000 500,000	(20) (60) (29)	No anticoagulant .. No anticoagulant .. No anticoagulant 3	.. .. 	 109
16	M	44	13	Staph. albus	?	100,000 100,000 to 200,000 180,000 100,000 to 400,000 (12 days at 400,000)	(11) (20) (7) (26)	Dicumarol §	4	64
18	M	53	6§§	Str. viridans	0.04	100,000 200,000 500,000 2,000,000	(2) (4) (33) (50)	Heparin **	1	89

* From date of first significant symptoms to beginning of course of penicillin which resulted in recovery. Cultures from the blood before such a course were positive for organisms regardless of previous penicillin therapy.

† By "course" is meant a period of treatment of seven days or more, separated from the next course by at least seven days.

‡ Continuous intravenous drip by the method outlined in the text and interrupted intramuscular injection were the methods used.

§ Used during first half of last course only.

determination of erythrocyte fragility and capillary fragility, and cultures of material from the nose and throat. Roentgenograms of the chest at 2 meters, electro-cardiograms and dental roentgenograms of the whole mouth were made. Electro-

. cardiograms were repeated at weekly intervals. The roentgenograms of the chest at 2 meters was repeated at the patient's discharge. Blood cell counts, urinalyses, determinations of the sedimentation rate and cultures of the blood were made frequently. Penicillin serum levels were determined and urinary excretion studied

Recovered Patients

Total Units of Penicillin	Method of Administration ‡	Combined Sulfonamide Therapy	Complications	Time Elapsed Since Recovery at End of Last Course of Treatment as of Feb. 15, 1947, Mo.	Status as of Feb. 15, 1947
20,337,000	Intravenous Intravenous Intravenous	Sulfamerazine Sulfadiazine	Splenic infarct	32	Compensated; doing light housework
5,600,000	Intravenous	None	None	35	Compensated; working 8 hr. day as chemist
8,300,000	Intravenous	None	Broca's aphasia; recovery	33	Compensated; working 8 hr. day at semisedentary work
....	Intravenous	Sulfapyridine	Pulmonary embolism (?)		
22,600,000	Intravenous	Sulfapyridine	....	26	Compensated; doing light housework
16,800,000	Intravenous	Sulfapyridine	None	26	Compensated; doing housework
18,400,000	Intravenous	Sulfapyridine	None	25	Compensated; doing light farm work
.... 15,066,000	Intramuscular Intravenous	.... Sulfapyridine	....	25	Compensated; doing normal schoolwork
.... 32,800,000	Intramuscular Intramuscular Intravenous	Sulfadiazine .... Sulfapyridine	Phlebitis in the left leg	24	Compensated; 8 hr. day doing office work
12,760,000	Intravenous	None	Pulmonary and cerebral embolism	28	Compensated; 8 hr. day doing office work
117,100,000	Intravenous	None	None	21	Compensated; continuing office practice (physician)

** Used during fortieth to fifty-first and sixty-seventh to seventy-eighth days of treatment only.
†† Cultures from the blood were sterile and sedimentation rates normal for four months after termination of the first course; then the patient relapsed or was reinfected.
§§ The patients in cases 10 and 11 were given second courses at increased dosage, because of rising sedimentation rates. In case 18 the daily dose was increased to 2,000,000 units because, although cultures of the blood were sterile, the clinical condition was extremely poor.

on many of the patients. A high caloric, high protein, high vitamin diet was given. In addition to administration of a multiple vitamin capsule of high potency, 100 mg. of thiamine hydrochloride, 50,000 units of vitamin A and 500 mg. of

Table 2.—

Case; Sex; Age, Yr.	Duration of Disease Before Any Penicillin Therapy, Wk.	Organism	Sensitivity to Penicillin, Units/Cc.	Daily Dose of Penicillin	Anticoagulants	Number of Courses of Penicillin	Total Days on Penicillin	Total Units of Penicillin
1 F 36	29	Str. viridans	0.02	Less than 200,000 (60 days) 200,000 (40 days)	Heparin *	16 †	100	17,559,500
2 F 17	11	Streptobacillus moniliformis	0.6	200,000 (5 days) 400,000 (14 days)	No anticoagulant	1	19	6,308,200
6 F 33	30	Str. viridans	0.04	200,000 (29 days) 300,000 (26 days)	Heparin Dicumarol	2	56	13,000,000
7 F 48	26	Str. viridans	0.02	200,000 (25 days)	Heparin	1	25	5,200,000
9 M 65	9	Str. viridans	0.08	225,000 (28 days) 300,000 (27 days)	Dicumarol Heparin	2	55	14,425,000
12 F 34	42	Str. viridans	0.04	400,000 (30 days)	No anticoagulant	1	30	12,000,000
13 F 23	12	Str. viridans	0.04	100,000 to 200,000 (47 days) 300,000 to 400,000 (35 days) 500,000 (38 days) 980,000 (21 days) 1,000,000 (6 days) No penicillin (15 days) 2,000,000 (38 days) 1,000,000 (4 days)	No anticoagulant	2	204	144,305,000
17 M 69	25	Str. viridans	0.1	500,000 (29 days).	No anticoagulant	1	29	14,500,000
19 F 41	41 §	Str. viridans	1.0	300,000 (10 days) 200,000 (11 days) 250,000 (3 mo.) 500,000 (9 days)	Heparin ††	4 **	130	27,000,000
20‡‡ F 24	30 to 52	Staph. aureus	? §§	500,000 (8 days)	Heparin	2	8	4,000,000

* During last nineteen days of illness only.
† From one to four days elapsed between "courses," except between numbers 15 and 16, when seven days elapsed (see fig. 4).
‡ During two "courses" only.
§ Before admission to our service.
** Beginning about three months after onset, patient received three of the courses elsewhere.

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Method of Administration	Combined Sulfonamide Therapy	Clinical Complications	Postmortem Findings
Intravenous Intramuscular	Sulfadiazine ‡	Hemiplegia; infarcts of spleen and kidneys; bowel hemorrhage	Fibrous vegetations of moderate size covered with fibrin on the mitral valve; bacteria present
Intravenous Intramuscular Intrathecal	None None	Encephalopathy; choked disk	Fibrous vegetation of moderate size covered with fibrin on the mitral valve
Intravenous	None	Hemiplegia (recovery); infarcts of spleen and kidneys	Apparently healed vegetations of mitral valve; scarring and ulceration of left auricular wall; bacteria present
Intravenous Subcutaneous	None	Pulmonary embolism; atelectasis	Large vegetation on aortic valve; two vegetations at the base of pulmonary artery; all fresh and containing bacteria
Intravenous	None	Encephalopathy; uremia	Fibrous nodules on the mitral valve; ulcer on the tricuspid valve; microscopically still active, with bacteria
Intravenous	None	Congestive failure	Grossly completely healed mitral lesion; ruptured chordae tendineae; involvement of left auricular wall; microscopic thin layer of fibrin; no bacteria
Intramuscular Intravenous	Sulfapyridine	Renal infarcts; cerebral hemorrhage	Two small vegetations of mitral valve, grossly not active; involvement of left auricular wall; bacteria in lesion of the valve
Intramuscular Intramuscular Intramuscular Intravenous Intravenous			
Intravenous	None	Staph. aureus septicemia, terminal, after apparent cure of Str. viridans endocarditis	Several small red elevated areas on mitral valve; microscopically almost healed vegetations with fresh acute inflammation and masses of cocci
Intravenous Intravenous Intramuscular Intravenous	None	Congestive heart failure	No autopsy
Intravenous	None	Cerebral embolism; auricular fibrillation; congestive failure	No autopsy

†† Begun on the sixth day of therapy.
‡‡ For about three weeks prior to admission to our service this patient received penicillin in daily doses of 100,000 to 200,000 units intramuscularly, together with sulfadiazine. Figures given refer to therapy on our service only.
§§ The original culture was lost before titration was done. Cultures of the blood after administration of penicillin was started were sterile.

ascorbic acid were given daily. We believe that such supportive treatment is important in a relatively chronic wasting disease of this type.

The patients were unselected. No patient was refused treatment because of duration of illness or apparent hopelessness of condition.

AGE AND SEX INCIDENCE

The ages 8 to 74 are represented. The distribution according to decades is as follows: Forty-seven per cent fall into the two decades from 21 to 40, and 65 per cent fall within the decades from 21 to 50. There are 18 females and 16 males.

ETIOLOGIC FACTORS

In 22 cases (65 per cent) a definite history of infection of the upper respiratory tract, which merged into the symptoms of bacterial endocarditis, was obtained. In 3 patients the symptoms followed extractions of the teeth. Two of these had concomitant infections of the upper respiratory tract. It is generally accepted that some previous valvular damage is necessary to the development of subacute bacterial endocarditis. However, a definite or suggestive history of such could be obtained in only 19 cases (56 per cent). On the other hand, in all hearts examined at autopsy evidence of previous valvular damage was present.

VALVULAR INVOLVEMENT

In the patients who recovered the determination could only be clinical, but since the antemortem determination of valvular involvement was found to be correct in all patients on whom autopsies were performed (10 out of 12), we believe the clinical determination to be reasonably accurate. Valvular involvement was distributed as follows: mitral valve 27, or 80 per cent; mitral and aortic valves, 1, or 3 per cent; aortic valve 5, or 14 per cent, and mitral and tricuspid valves 1, or 3 per cent. One patient with aortic involvement also had vegetations in the root and ascending portion of the pulmonary artery (case 6).

BACTERIOLOGY

Organisms isolated included Streptococcus viridans (24 patients), Streptococcus haemolyticus (3 patients; in 1, non-green-producing, but only weakly hemolytic), nonhemolytic (gamma) streptococci (2 patients), Staphylococcus aureus (2 patients), Staphylococcus albus (1 patient), Streptobacillus moniliformis (1 patient) and Hemophilus parainfluenzae (1 patient).

The percentage of organisms (29 per cent) other than Str. viridans is higher than that usually reported.

Cultures of the blood were made routinely on admission, tests being made for both aerobic and anaerobic organisms and several different

mediums being employed for each procedure. Cultures were not reported as sterile unless there was no growth after fifteen days' incubation. When a culture was positive for organisms, the medium and procedure which had resulted in the best growth of the organism was used for subsequent cultures of the blood. Penicillinase [2] was added to the blood for culture to prevent false negative results due to penicillin in the blood. However, we have not obtained a culture yielding organisms from penicillinase-treated blood when sterile cultures resulted from the same sample of blood without penicillinase.

Adequate cultures of the blood permit early recognition of the disease and the institution of therapy before the pathologic processes have progressed too far. These should be made on all patients who do not recover promptly from simple infections of the upper respiratory tract, extractions of teeth, tonsillectomy and other minor ailments, particularly in patients known to have cardiac damage, however slight. It is our

TABLE 3.—*Concentration of Penicillin Required to Inhibit Growth of Organism in Vitro*

Seven organisms were lost before titration was done.

	Recovered	Deaths
0.06 units/cc. and under	7	5
0.07 units/cc. and over	9	5

conviction that the real solution of the problem of bacterial endocarditis lies in the prompt and adequate treatment of all known bacteremias plus the prophylactic use of penicillin in extraction of teeth and in every case of infection of the upper respiratory tract or any other infection in patients suspected of having valvular involvement.

After the organism was recovered and identified, it was titrated for sensitivity to penicillin according to the method of Hobby.[3] Results of tests for sensitivity in 26 cases ranged from 0.02 to 6.0 units per cubic centimeter. We have found the in vitro sensitivity to be only a rough guide of the daily requirements of dosage. The relationship between results of therapy and in vitro sensitivity to penicillin is shown in table 3. It is seen that in vitro sensitivity of the organism to penicillin is not per se significant as regards ultimate success of therapy. Previous duration of the disease and adequacy of the dosage of penicillin are more important prognostically than the in vitro sensitivity of the organism.

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2. At first taka diastase (a proprietary starch digestant) was used and later penicillinase furnished by Schenley Research Laboratories.

3. Hobby, G. L.; Meyer, K., and Chaffee, E.: Activity of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. **50**:277 (June) 1942. Later a modification of the method of Heilman and Herrell was used.[1a]

Except when the organisms were of extremely high in vitro resistance, cultures of the blood usually became sterile within six to seventy-two hours after treatment with penicillin was started and remained so throughout therapy, regardless of whether or not the initially selected dosage was adequate for ultimate cure. The lack of significance of sterile cultures of the blood in judging response to therapy and adequacy. of dosage will be discussed later.

METHODS OF ADMINISTRATION

Realizing at the onset that mere sterilization of the blood stfeam would probably not in itself be adequate for a cure in a disease in which bacteria are enmeshed

Fig. 1.—Needle anchored in small vein of forearm. Adapter and rubber tubing fixed to permit freedom of movement of forearm.

in fibrin and knowing from our own studies and those of others[4] that single doses of penicillin were rapidly excreted, with consequent rapid lowering of the blood level, it seemed logical that the maintenance of as constant a blood level as possible as well as one in excess of the in vitro sensitivity of the organism would be necessary. We therefore selected continuous intravenous drip as the method of administration most likely to insure a favorable result.

The day's dose of penicillin is dissolved in a liter of isotonic solution of sodium chloride and the rate of flow adjusted so that this amount is delivered in twenty-four hours.

4. Rammelkamp, C. H., and Keefer, C. S.: Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**:425 (May) 1943.

The method which we have found most satisfactory[5] has been described previously (fig. 1). It allows the needle to remain in situ for two weeks or longer without appreciable discomfort to the patient. Venous irritation and thrombosis did occur but were relatively infrequent. Five per cent dextrose or distilled water should not be used, since they promptly lead to such occurrences. The possibility of pulmonary embolism resulting from continuous venoclysis must be considered. However, since only 3 of the 12 patients on whom autopsies were performed had pulmonary emboli, which in all 3 could have been due to other conditions, we believe that the possibility is remote.

Recently we have been using a sodium salt containing 90 per cent penicillin X,[6] and so far there seems to be less venous irritation and thrombosis than with the regular sodium salt of various manufacturers. The same seems to be even more
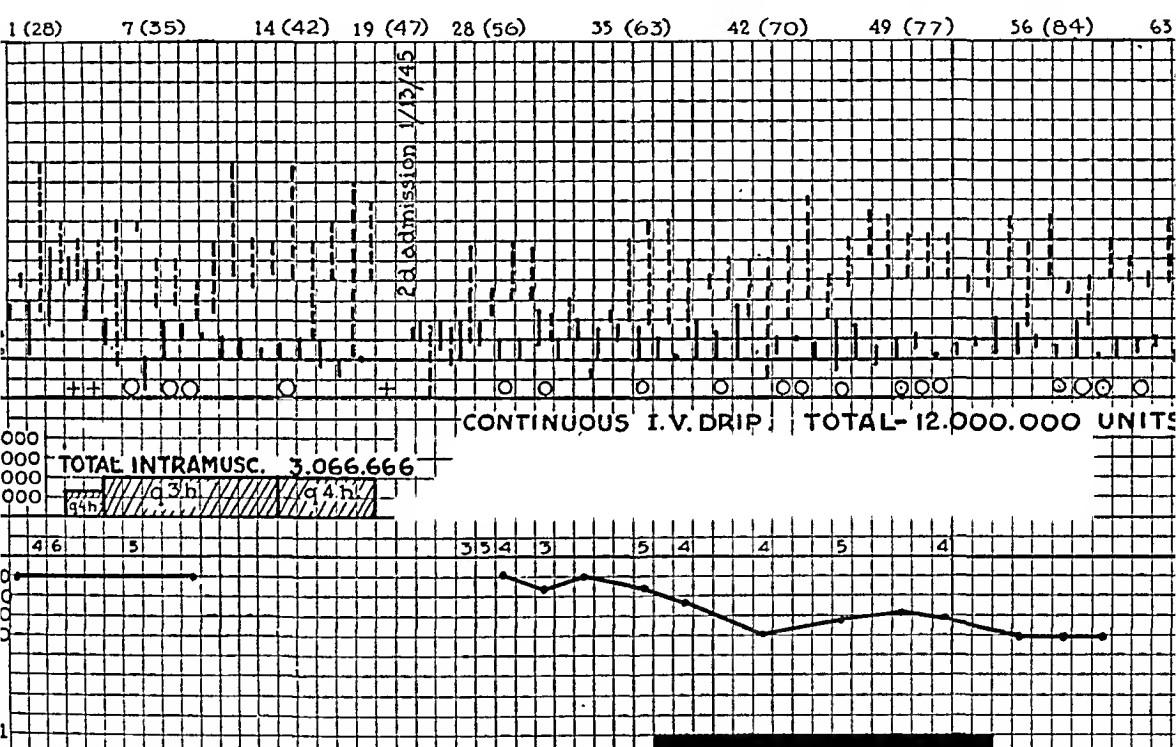
Fig. 2 (case 14).—J. W., aged 14 years, was admitted to the hospital Dec. 20, 1944, with a diagnosis of subacute bacterial endocarditis caused by Str. viridans. Figures in parentheses indicate the approximate days of illness.

definitely true of juxtacrystalline penicillin sodium containing 1,600 units per milligram.[7] The calcium salt (supplied by Schenley Laboratories, Inc.) also produces minimal venous irritation.

We are aware that cures have been and undoubtedly can be obtained by interrupted intramuscular injection even at three hour intervals. But from our experience to date, we believe that the highest percentage of cures will be obtained by

5. Priest, W. S.: Penicillin Therapy, Am. J. Surg. **67**:280 (Feb.) 1945. Herrell, W. E.: The Clinical Use of Penicillin, an Antibacterial Agent of Biologic Origin, J. A. M. A. **124**:622 (March 4) 1944.

6. Supplied by Lederle Laboratories, Inc.

7. Furnished by Commercial Solvents Corporation.

use of continuous intravenous drip. Cases 14 and 15 illustrate this point (figs. 2 and 3).

Permanently sterile cultures of the blood were not obtained in either case with intermittent intramuscular administration of daily doses of 300,000 to 500,000 units for prolonged periods. Cure was effected with continuous intravenous therapy. In addition, 3 other patients were cured following continuous intravenous therapy after failure had resulted on intramuscular injections of presumably adequate dosage and duration (300,000 units or more daily).

The serum penicillin levels obtained with similar daily doses administered by the two methods to the same person further suggest the apparent greater efficacy of continuous intravenous drip.
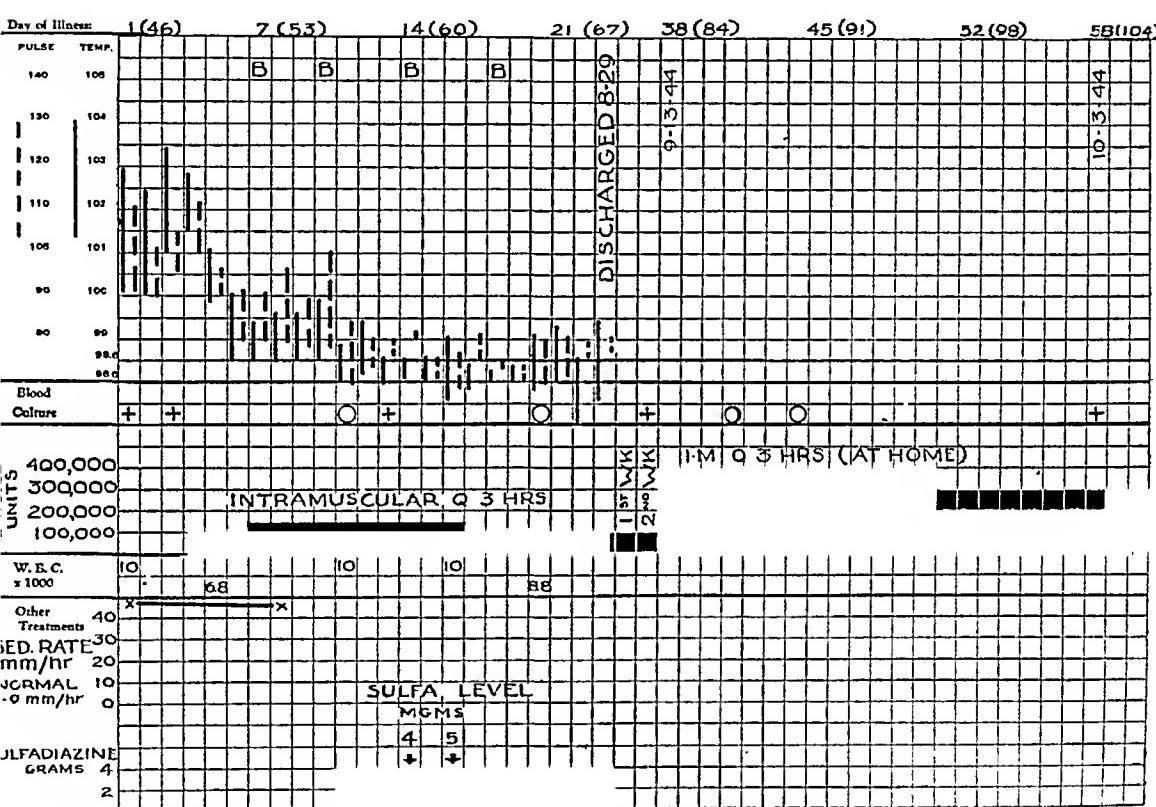
Fig. 3 (case 15).—M. K., aged 29, was admitted to the hospital on Aug. 7, 1944 with a diagnosis of subacute bacterial endocarditis caused by weakly hemolytic streptococci having a sensitivity to penicillin of 0.02 unit per cubic centimeter. B indicates transfusions of 500 cc. of whole blood. Figures in parentheses indicate the approximate day of illness.

In all but 2 of the successfully treated patients, so far, serum penicillin levels of at least 1 unit per cubic centimeter were found to be necessary. The level might occasionally fall to 0.5 unit per cubic centimeter, but if this level persisted for any length of time unfavorable clinical signs developed. In several instances favorable results could not be obtained until much higher levels were reached and maintained. When a single intramuscular injection of up to 80,000 units is given, the serum level rises rapidly to reach a maximum in about ninety minutes. From that point it falls rapidly, within thirty to forty-five minutes, to zero. Hence, in a three hour schedule of a daily dose up to 640,000 units there is a period of from

forty-five minutes to one hour out of every three when the serum level is below even the in vitro requirements for inhibition of the organism. Bacteriologic evidence of the possible importance of the period when the level is at zero, which occurs with intramuscular injection every three hours, was observed in our first patient (fig. 4). Daily cultures of the blood at various hours during the period of continuous intravenous drip failed entirely to yield organisms, while cultures taken three hours after an intramuscular injection occasionally produced them. This figure also illustrates the immediate and continuously sterile cultures of the blood obtained during administration of penicillin in dosages inadequate for cure. At autopsy, bacteria-filled fibrin was present on the incompletely healed valve. In this case the dose of penicillin remained the same for each period.
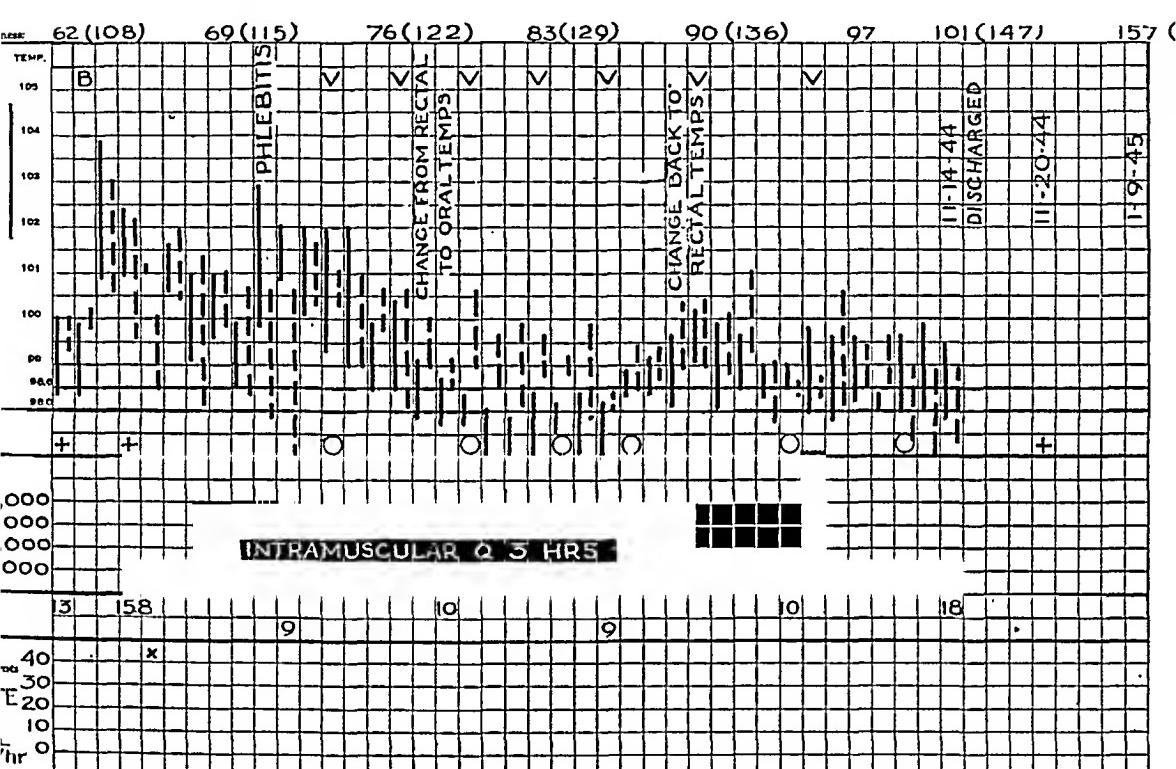
Fig. 4 (case 15).—The patient (fig. 3) was readmitted on Oct. 6, 1944. *V* indicates autovaccine. *B* indicates transfusion of 500 cc. of whole blood. Figures in parentheses indicate the approximate day of illness.

With administration of individual doses of 150,000 to 350,000 units, the outline of the serum penicillin curve is similar, but the maximum level is higher; the two hour level is usually theoretically adequate (1 to 2 units per cubic centimeter), and subminimal or zero levels are not reached until about three hours after injection. When 5 or 10 per cent dextrose in isotonic solution of sodium chloride is used as the diluent, the curves are the same so far as the duration of subminimal or zero levels is concerned. The maximum level, however, may be one and a half to two times as high as when the same dose is given in isotonic solution of sodium chloride to the same patient. The foregoing observations have been repeatedly confirmed. In 1 patient with renal insufficiency the lowest serum level with administration of 50,000 units every two hours was 2.0 units per cubic centimeter. This suggests the desirability of using diodrast or para-aminohippuric acid when interrupted intramuscular injection is the only feasible

method of administration. However, it seems more practical to use larger doses, 100,000 units or more, at intervals of not less than two hours and preferably at intervals of ninety minutes.

Determinations of the serum level done on the same patients when receiving penicillin by continuous intravenous drip in daily doses comparable to those given by interrupted intramuscular injection (300,000 to 2,000,000 units) show an absence of the high peak and the periods of subminimal or zero levels. There is some fluctuation, seldom exceeding 1 unit per cubic centimeter. Even with the smaller doses (300,000 to 350,000 units per day) the lowest level seldom is below 0.5 unit per cubic centimeter. Curves on the chart of the same patient on varying daily doses have the same features but at different levels. Doubling of the daily dose does not necessarily mean doubling of the mean serum level. The relatively constant serum levels obtainable by continuous intravenous drip constitute, we believe, the most important argument in favor of this method.

In doing these experiments, it was demonstrated that a relatively constant intake of fluid resulted in less fluctuation of the serum level, regardless of the method of administration. This led us to limit the oral intake of fluid to 800 cc. daily, given at the rate of 100 cc. every two hours from 7 a. m. to 9. p. m.

Continuous intrasternal infusion was tried on 1 patient who had previously received continuous intravenous drip. On the same daily dose comparable and equally constant blood levels were obtained. But after forty-eight to seventy-two hours the needle bcame loose. The method proved more uncomfortable for the patient.

Continuous subcutaneous infusion was used for thirteen out of twenty-five days of total treatment in 1 patient (case 7). Sterile cultures of the blood were obtained during this period; yet at autopsy the most active lesion of all was found. Unfortunately, studies of the blood level were not made on this patient. The organism was of the most sensitive group (0.02 unit per cubic centimeter).

Oral therapy, hourly dosage of 100,000 units of the preparations of penicillin then available being employed, failed to produce adequate blood levels, sterile cultures of the blood or the desired clinical improvement.

Intratibial infusion, because of the mechanical difficulties encountered, was abandoned, though it would apparently meet all criteria. In one out of five attempts it was successfully used for two weeks, producing blood levels equal to those obtained from continuous intravenous drip in the same patient.

DOSAGE AND DURATION OF TREATMENT

No uniformity of opinion exists as yet as to dosage and duration of treatment required. The facts relative to 20 patients in this series are set forth in tables 1 and 2. Regardless of other factors involved, cures resulted in only 2 cases from a dose of 200,000 units per day.

When the "courses" of treatment of less than three weeks' duration are excluded, these 20 patients received a total of forty-six courses, including those received prior to admission to our service. Twenty-one of these courses (45 per cent) were inadequate, regard less of dosage. Of these, 52 per cent were at the level of 200,000 to 250,000 units per day, 23 per cent at 300,000 units, 4 per cent at 400,000 units, 14 per cent at 500,000 units and 4 per cent at 2,000,000

units. Thus 75 per cent of the inadequate courses of treatment concerned doses ranging from 200,000 to 300,000 units per day. For this reason it is our opinion that administration of any daily dose less than 400,000 units is not conducive to the highest over-all percentage of cures. Further evidence that between 400,000 and 500,000 units per day is the minimal safe dose is the fact that 7 out of the 10 patients who recovered required this dose, after failing to respond to doses of 200,000 to 300,000 units, and 5 (50 per cent) of the deaths occurred in patients receiving 200,000 to 400,00 units per day and 3 in those receiving 500,000 units. These observations led us to adopt 500,000 units per day as the minimal initial dose when continuous intravenous drip is the method of administration.

The importance of adequate daily dosage from the outset is again stressed by comparison of the percentage of recoveries in our first and second groups of 20 patients. If from the first group we exclude the patient (case 12) who died of congestive failure but showed histologic evidence of cure and the 2 (cases 19 and 20) who lived only nine and eight days after being admitted to our service and on whom permission for autopsy could not be obtained and compare the rate of recovery with the first 17 of our second group of 20 patients, all of whom were started on 500,000 or more units per day, we find that 59 per cent of the first group are alive after twenty-one to thirty-five months and 88.2 per cent of the second group after thirteen to twenty months. Thus in the first group, in which 41 per cent died, all but 1 of those who died received less than 500,000 units per day, while in the second group in which only 11.8 per cent died, the daily dose was never less than 500,000 units and frequently 1,000,000 or 2,000,000 units. Duration of the disease prior to therapy and complications in the two groups were comparable.[8]

That the use of daily doses of less than 400,000 units has its unfavorable economic side is indicated in table 4, which shows the total units of ineffective or wasted penicillin and the total number of days in the hospital during which treatment was ineffective or wasted among 7 recovered patients who had received such dosage without favorable results.

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8. In vitro penicillin sensitivity of causative organisms was, on the whole, higher in the second group than in the first. Recovery was 100 per cent in cases 23 to 38 inclusive. The daily dosage adequate for recovery was 500,000 units in 4 patients and 1,000,000 units in 10 patients. Five instances of failure with 500,000 units per day are recorded. Recovery followed the use of larger doses. Two patients who failed to respond to daily doses of 1,000,000 and 2,000,000 units of penicillin recovered after administration of streptomycin. (Priest, W. S., and McGee, C. J.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **132**:124 [Sept. 21] 1946).

Our material does not permit of any definite conclusions as to the minimal optimum daily · dose by interrupted intramuscular injection. From observations in cases 13, 14 and 15, from the failures which have resulted in our cases after long courses of 300,000 to 500,000 units per day and from our studies of serum penicillin levels following interrupted intramuscular injection, we should not feel safe in starting treatment with less than 800,000 to 900,000 units per day, divided into twelve or eighteen injections, when administration must be by this method.

One reason for the wide discrepancy in opinion as to what constitutes an adequate daily dose may lie in the wide variation of serum penicillin levels obtained in different patients from the same dose by whatever method given. In all our patients so far we have not observed

TABLE 4.—*Relation Between Daily Dose of Penicillin and Duration of Treatment in Cases of Recovery*

1. Average number of total days of treatment of patients started on less than 400,000 units per day	70
2. Average number of days of unsuccessful treatment with doses less than 400,000 units per day	43
(a) Maximum number of days of treatment before dose was increased to 400,000 or more units per day	168 *
(b) Minimum number of days of treatment before dose was increased to 400,000 or more units per day	6
3. Average number of days of treatment required for cure after administration of 400,000 or more units per day was started	32.0†
(a) Maximum	83.0
(b) Minimum	12.0
Total units of penicillin given without effect (round figures)	63,000,000
Total number of days in hospital during which treatment was ineffective	149
(The patient receiving one hundred and sixty-eight days of ineffective treatment was treated at home for one hundred and fifteen days)	

* During this period, this patient had thirty-six days at 400,000 units per day by interrupted intramuscular injection every three hours without securing permanently sterile cultures of the blood. Recovery occurred after thirty days at 500,000 units by continuous intravenous drip (case 15; fig. 3).

† When the 1 person (case 18) treated for eighty-three days continuously is omitted, the average is twenty-seven days.

a single cure in which the mean serum level was not considerably above 0.5 unit per cubic centimeter; yet only eight of twenty-six organisms titrated required more than 0.1 unit of penicillin per cubic centimeter for in vitro inhibition. The most obvious reason we can see for this discrepancy is the necessity for penicillin to penetrate deeply into the fibrin of the vegetative processes in order to inhibit the bacteria lodged there and the assumed lowering of concentration of the penicillin during such penetration.[9] That mere sterilization of the blood stream is not sufficient for a cure is now well established. Hence it would seem entirely possible to have in one series of patients a majority in

9. Since this article was written, experimental proof of this has been offered (Nathanson, M. H., and Liebhold, R. A.: Diffusion of Sulfonamides and Penicillin into Fibrin, Proc. Soc. Exper. Biol. & Med. **62**:83 [May] 1946).

whom adequate blood levels could be obtained with administration of 400,000 units per day or possibly less, while in another series adequate levels for the majority could be obtained only with administration of doses of 400,000 or more units per day. Since few physicians have the facilities or time to determine serum penicillin levels, it would seem all the more important to allow as much as possible for these variables and to start treatment with administration of a daily dose of at least 500,000 units.

How long treatment should be continued is another point on which all are not agreed. Having seen the degree of activity and the bacteria present in the lesions of 8 of the patients who died in this series and knowing that all 8 patients had had treatment from twenty days to several months and having observed in the patients who recovered that an average of twenty-seven days was required for clinical evidence of cure after adequate daily dosage was reached, we have adopted four weeks as the minimum duration of therapy. With one exception, anything less than four weeks of treatment has resulted in failure, regardless of dosage used. If clinical signs are not favorable at the end of this time, treatment is continued regardless of how many weeks it takes.[10]

The patients in cases 13 and 18 are the only ones of the first 20 to whom doses larger than 500,000 units per day were given. The patient in case 18 was doing badly clinically after thirty-three days at 500,000 units per day. The organism was relatively sensitive (0.04 unit per cubic centimeter) and duration of disease short (about eleven days). Whether a daily dose between the 500,000 units which was inadequate and the 2,000,000 units which resulted in a cure would have sufficed, we do not know. That the patient in case 13 should have had fibrin and masses of viable bacteria after eight months of treatment, forty-two days of which were at 2,000,000 units per day, remains an enigma.

The organisms from these 2 patients were typed as Streptococcus s.b.e.,[11] a strain of Str. viridans which is apparently peculiarly resistant to penicillin in vivo. Of the 7 patients whose organisms were typed as Str. s.b.e., 5 died. Our experience, as well as that of others,[11] indicates that when this strain is being dealt with the daily dose should be not less than 2,000,000 units.

These experiences have led us to take the position that if after four to six weeks' administration of 500,000 units per day

10. The average duration of treatment in cases 23 to 34 inclusive was fifty-seven days. This group included 4 patients in whom the situations were apparently hopeless at the outset of treatment. All recovered.

11. Loewe, L.; Plummer, N.; Niven, C. F., Jr., and Sherman, J. M.: Streptococcus s. b. e. in Subacute Bacterial Endocarditis, J. A. M. A. **130**:257 (Feb. 2) 1946.

by continuous intravenous drip the patient is not doing well clinically, then the dose is increased to 2,000,000 units per day. Subsequent experience may show that such a radical increase is not necessary, but from our evidence so far we are loath to do anything else. If the in vitro sensitivity of the organism can be determined before treatment is begun and it is found to be 1 unit or more per cubic centimeter, we start with administration of 1,000,000 units per day and do not hesitate to increase to 2,000,000 units and even higher doses per day if the clinical course is unfavorable.

Until more information is available on the relationship between duration of disease and response to therapy, we cannot say definitely how much this factor should influence the determination of the daily dose. The duration of disease in our patients who recovered up to the time of the course which resulted in recovery averaged sixteen and eight-tenths weeks, and that in the fatal cases to the time of initial penicillin therapy averaged twenty-two and one-half weeks. Our experience dictates that the minimal initial dose should be 500,000 units per day in any case and 1,000,000 units a day for any patient with a duration of disease of over twelve weeks.

REACTIONS

Thirteen of our first 20 patients had one or more reactions in the form of hyperpyrexia during therapy. These consisted of sudden severe chill with sharp rise in temperature to 103 up to 105 F. The return to normal always occurred within twelve hours. There was no relationship to the brand of penicillin used. The transferring of the penicillin and isotonic solution of sodium chloride, rubber tubing and needle intact to another patient failed to produce a reaction in the second patient. Hence it was concluded that it could not be due to pyrogens. The dosage of penicillin per se was not the cause, since reactions occurred with administration of 200,000 units per day as well as with 1,000,000 units per day. Two patients (cases 8 and 10) had several reactions during their first course at 200,000 units per day but had none during a second course at 400,000 units per day. Another patient (case 6) had none on a daily dose of 200,000 units but had several during a second course at 300,000 units per day, initiated several weeks later. Other patients in whom more than one level of dosage was used had reactions at both levels. It is of interest, although of doubtful significance, that of the patients who recovered (clinically and histologically) 73 per cent had these reactions while of those who failed to recover only 55 per cent had these reactions. One cubic centimeter of serum obtained from a patient at the height of a reaction and reinjected during an afebrile period produced the same type of reaction in a most violent form, whereas her "normal" serum did not. This

would seem to indicate an individual anaphylactoid phenomenon. Febrile reactions have not occurred in our latest 13 patients even with administration of doses up to 2,000,000 units per day. This suggests that something in the earlier penicillin salts which is not now present may have been the cause. Except in 1 case, we could not detect any harm to the patient by these reactions and did not discontinue treatment.

Urticaria was observed once (case 8). This was at the outset of a second course of treatment instituted because of a relapse after five months of apparent cure. It was not widespread, treatment was not discontinued and the urticaria disappeared within a few days.

A disconcerting type of reaction, encountered four times thus far, is abdominal pain, sometimes of great severity, associated with tenderness, usually generalized, rigidity and distention. In all instances careful examination failed to reveal any intra-abdominal, gastrointestinal or renal lesion, and the symptoms promptly subsided on withdrawal of penicillin. From our meager experience with this reaction it appears possible to resume therapy after a few days, without recurrence of reaction.

COMBINATION THERAPY

None of the strains of Str. viridans encountered in all our patients to date has been inhibited in vitro by any of the sulfonamide drugs. In cases 1, 3 and 15 sulfadiazine was used in full therapeutic doses without affecting the cultures of the blood. The patient in case 3 also had a short course of sulfamerazine. The patients in cases 3, 8, 10, 11, 14 and 15 of the group which recovered had subtherapeutic doses (1 to 2 Gm. per day) of sulfapyridine during penicillin therapy. In these patients recovery followed the course of penicillin in which such doses of sulfapyridine were also given. However, in each instance the daily dose of penicillin was also increased; hence it cannot be said that the addition of the sulfapyridine was a deciding factor in recovery. No synergistic effect was observed when the organisms from several of these patients were subjected in vitro to combinations of penicillin and various sulfonamide compounds in varying concentrations.

From these in vitro tests and from the several instances in which sulfonamide drugs were of no help when used in connection with doses of penicillin later proved to be inadequate, we are of the opinion that, so far as Str. viridans is concerned, the use of sulfonamide drugs in connection with penicillin is without value. In fact, we believe that the use of sulfonamide drugs is contraindicated because of the frequent involvement of the kidneys by the disease itself. However, that one must be on the lookout for the unusual organism which will respond only to combined administration of the two drugs is indicated by 1 of our patients whose organism belonged to the parainfluenzal group. Sterile cultures of the blood and clinical improvement could not

be obtained with eight weeks of administration of penicillin alone in doses up to 1,000,000 units per day. Sulfonamide therapy alone was equally ineffective.[12] Use of a combination of 500,000 units of penicillin and sulfamerizine to maintain a blood level of 10 to 22 mg. per hundred cubic centimeters for a period of forty-three days resulted in arrest of the disease. It is now seventeen months since completion of this combined therapy, and there have been no signs of relapse.

ANTICOAGULANTS

The use of anticoagulants (heparin as well as dicumarol [3,3'-methylene-bis-(4-hydroxycoumarin)]) proved of no demonstrable therapeutic value.[13] They exerted no influence on the dosage of penicillin, had no influence on the formation of fibrin, as shown in histologic studies, and did not affect the length of time over which therapy was required.

OTHER FACTORS IN RELATION TO SUCCESSFUL OR FATAL TERMINATION

As noted in the section "Method of Study," several collateral observations were made on the patients in this series. The total data on any one factor were found to be too small to permit of statistical evalution. The actual results will therefore be presented without much comment.

1. *Age.*—The average age at the time of beginning therapy of those who died was 39.0 years, and of those who recovered it was 33.5 years.

2. *Average Duration of Disease Before Administration of Penicillin.*—In those who died, the average duration was 22.5 weeks; in those who recovered it was 9.2 weeks. The latter figure loses much of its apparent significance when the average duration of disease among the patients with successful results is adjusted to the time of the final course of therapy which actually resulted in cure, when one bears in mind that up to that time the disease in these patients was bacteriologically or clinically active and that they would presumably have died had it not been for this final successful course. With such adjustment the figure becomes 16.8 weeks.

3. *Erythrocyte Count.*—In the fatal cases the average was 3,350,000 before administration of penicillin; in the cases of recovery it was 4,230,000.

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12. This organism was insensitive to any concentration of penicillin in vitro but was inhibited by a sulfonamide concentration of 3 mg. per hundred cubic centimeters. It was later found to be inhibited by streptomycin, which today would be the drug of choice for such an organism.

13. Priest, W. S.; Smith, J. M., and McGee, C. J.: The Effect of Anticoagulants on the Penicillin Therapy and Pathologic Lesion of Subacute Bacterial Endocarditis, New England J. Med. **235**:699 (Nov. 14) 1946.

4. *Leukocyte Count.*—The average in the fatal cases before administration of penicillin was 11,000; after administration of penicillin it was 13,700. The average in the cases of recovery before administration of penicillin was 8,880; after administration of penicillin, it was 9,200. In addition to suggesting that patients with a normal leukocyte count before therapy have a better prognosis than those with leukocytosis, it also emphasizes what will be stressed later—that a rise in leukocyte count occurring during or immediately after therapy is indicative of inadequate treatment unless some other definite cause can be found for the rise.

5. *Total Serum Protein Content.*—In all patients the total serum protein content was at or slightly below the lower limit of normal before penicillin therapy. In the fatal cases the average level remained unchanged, while in the cases of recovery there was a slight increase (averaging 0.64 Gm. per hundred cubic centimeters) after penicillin therapy.

6. *Albumin-Globulin Ratio.*—The albumin-globulin ratio was close to 1:1 or slightly dislocated in all patients before therapy. Little change occurred during therapy in either the cases of failure or the cases of recovery.

7. *Alkali Reserve.*—Slightly subnormal values were found in all patients before penicillin therapy. During therapy there was essentially the same rise in carbon dioxide–combining power (3.8 to 3.5) in both cases of failure and cases of recovery.

8. *Blood Chloride Levels.*—Blood chloride levels were within normal range in all patients before therapy.

9. *Electrocardiographic Changes.*—Serial records made during therapy showed a preponderance of changes in the patients who died. Of these, only 1 failed to show electrocardiographic changes. The observed changes (except those induced by digitalis) were shift in the electrical axis, inversion of the T wave in leads III and CF_2, changes in the T wave suggestive of coronary insufficiency, flattening of the T wave in all leads and the development of arrhythmias (auricular fibrillation and ectopic impulses). Serial records of 16 patients who recovered showed no change in 13, and changes in the T waves and RS-T interval in 3. From this it would seem that serial electrocardiograms are of value as an aid to prognosis and possibly in estimation of the degree of myocardial involvement during the course of the infection. To date, the hearts of the 3 recovered patients who showed electrocardiographic changes are not demonstrably less efficient than the hearts of those whose records showed no changes.

10. *Complications.*—As to renal, splenic, pulmonary and cerebral infarction, meningoencephalopathy, the development of cardiac arrhyth-

mias and thrombophlebitis (not caused by intravenous therapy) there was a total of fifty-seven such complications. Thirty-seven of these occurred in the patients who died. It is possible that small infarcts of the spleen, kidneys and lungs were missed in the patients who recovered whose records contained no evidence of such and in cases in which the patient's complaints did not suggest them. However, it seems safe to say that in cases in which the infarct is of sufficient size to cause clinically recognizable symptoms and signs and if such episodes are multiple, the prognosis is less favorable.

We wish to call particular attention to a cerebral complication we have observed twice. Signs of meningeal irritation develop. Intracranial pressure is increased to the point of papilledema. The spinal fluid is under increased pressure and the cell count and protein content are increased, but organisms are not found. Cranial palsy of the nerves, particularly of the oculomotor nerves, may occur. Headache, photophobia and dimness of vision were complained of, and vomiting occurred in both patients. A diagnosis of brain abscess, possibly multiple, was made. Yet at autopsy of 1 patient no abscess was found. Intraspinal injection of penicillin in doses up to 50,000 units daily had no effect on the course of the disease or the cerebral symptoms in this patient. Our belief that the daily intravenous dose of penicillin in this patient should have been at least 2,000,000 units is based on our experience with the second patient having similar symptoms. In this patient a diagnosis of brain abscess was also made, and unsuccessful attempts were made to localize it by ventriculography. Intracranial pressure became so great that decompression was necessary. With administration of adequate doses of penicillin (2,000,000 units per day) the patient progressed to recovery and, except for minor residual neurologic effects, appeared normal seventeen months after termination of therapy. Dr. Frederick Hiller, of the Department of Neurology, who examined most of our patients showing cerebral complications, stated the belief that these phenomena represented meningoencephalitis caused by multiple minute bacterial emboli. He expressed the opinion that in subacute bacterial endocarditis cerebral manifestations are the result of large emboli or metastatic mycotic encephalitis. The latter is more frequent and is caused by minute bacterial emboli. Appearance of areas of ischemia followed by acute inflammatory reaction and possibly hemorrhage result. The surrounding brain tissue is edematous. The clinical picture may vary from that of a sudden transitory aphasia or monoparesis to a hemiplegia. The ability of the brain to recover from this type of lesion is remarkable. Even complete hemiplegia may disappear in a few days, with little or no residuals. Showers of such bacterial emboli may produce coma, delirium and convulsions. Such lesions occurring in

the meninges add signs of meningitis to the picture, which may be further aggravated by hemorrhage into the subarachnoid space.

If recovery from hemiplegia is slow and significant residual paresis remains, the lesion is most likely an embolism of a larger arterial branch. If bacteria are present in such a major embolus, an abscess might develop. However, the relative avirulence of most organisms responsible for subacute bacterial endocarditis makes brain abscess extremely rare in this disease, and surgical treatment is almost never indicated. The
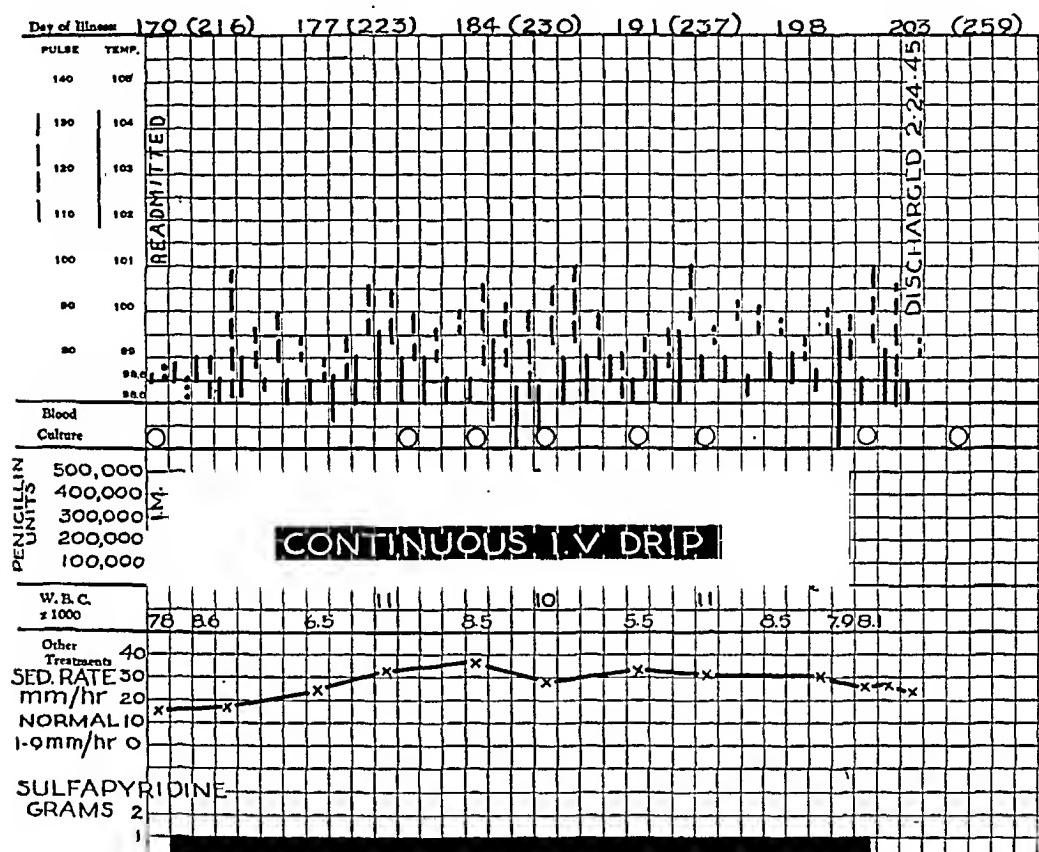
Fig. 5 (case 15).—The patient (figs. 3 and 4) was readmitted on Jan. 22, 1945. The figures in parentheses indicate the approximate day of illness.

condition calls for administration of large doses of penicillin (1,000,000 to 2,000,000 units or more per day).

CRITERIA FOR SUCCESS OF THERAPY

Any one undertaking penicillin therapy of subacute bacterial endocarditis for the first time is confronted with the problem of how much penicillin should be used, for how long and how it will be indicated that the patient is cured. Our opinions concerning dosage and average duration of treatment and the reasons therefor have already been set forth. The unreliability of sterile cultures of the blood, normal temperature and the patient's sense of well-being as criteria of success or
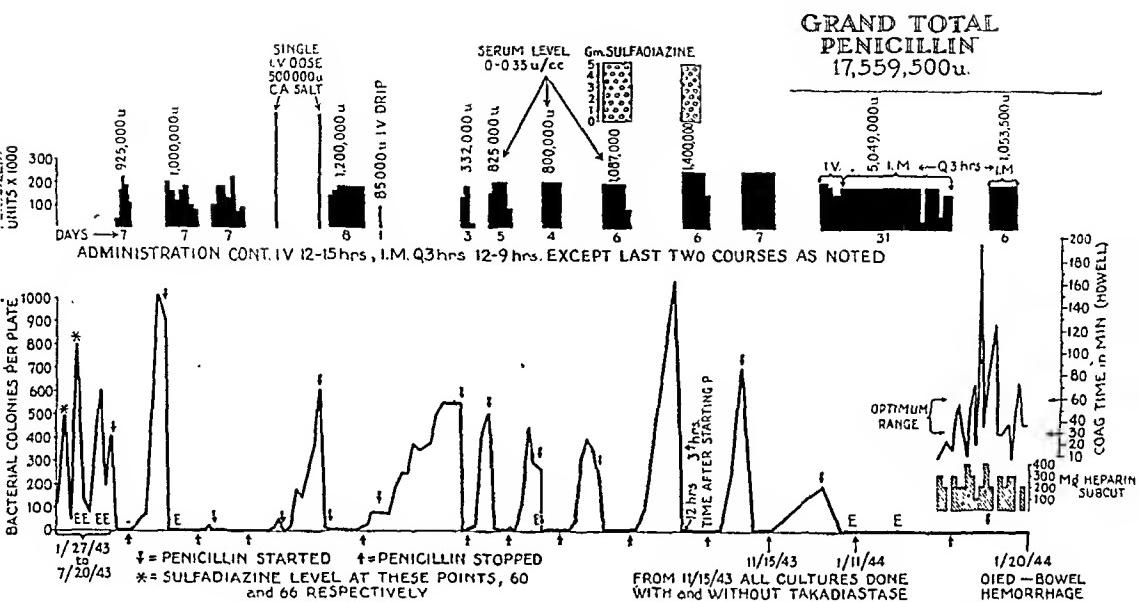
Fig. 6 (case 1).—Mrs. E. S. had subacute bacterial endocarditis caused by Str. viridans having a sensitivity to penicillin of 0.02 unit per cubic centimeter. *E* indicates visceral embolic phenomena.
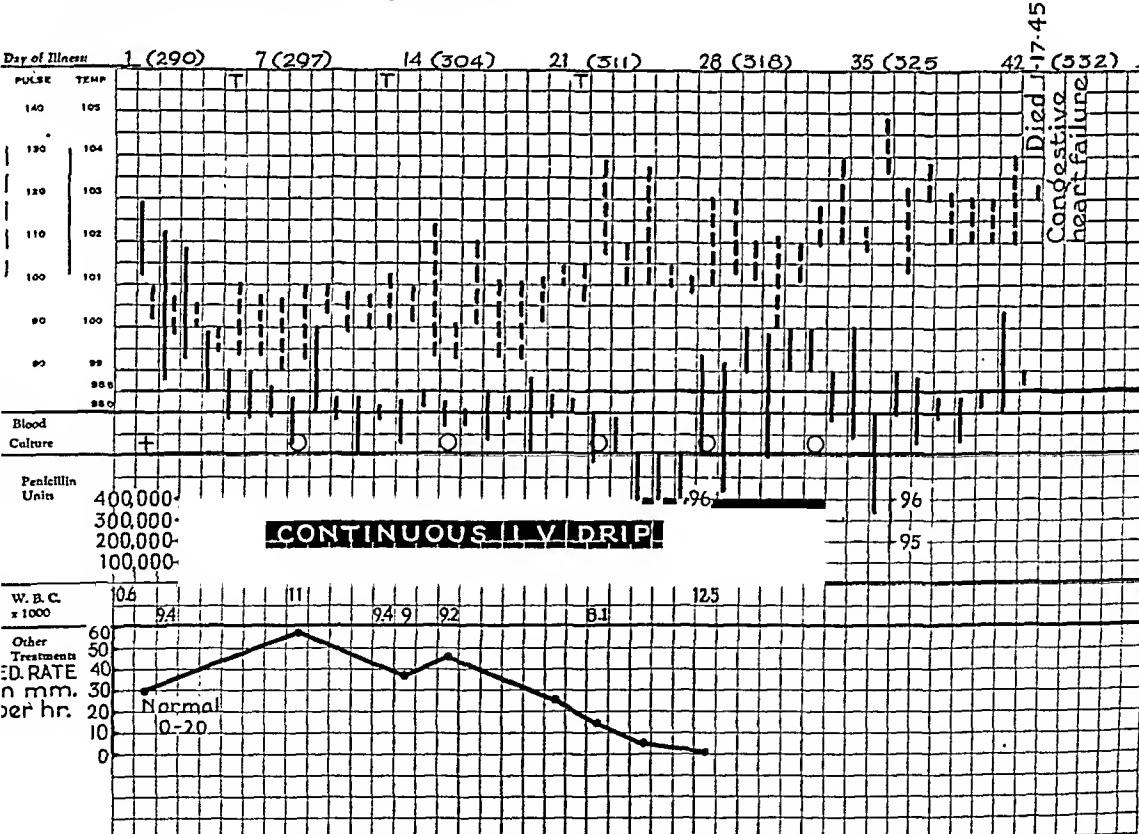
Fig. 7 (case 12).—Mrs. H. B., aged 34, was admitted to the hospital on June 12, 1944 with a diagnosis of subacute bacterial endocarditis caused by Str. viridans with a sensitivity to penicillin of 0.04 unit per cubic centimeter. *T* indicates blood transfusions of 500 cc. Figures in parentheses indicate the approximate day of illness.

adequacy of therapy have also been pointed out. Of course, a culture of the blood which produces organisms during therapy always means that the daily dosage is dangerously inadequate, since dosage may be inadequate though cultures of the blood become sterile. The only consistently reliable guides we have found after cultures of the blood have become sterile are the leukocyte count and the sedimentation rate.

As stated before, the leukocyte count in the fatal cases averaged 2,700 higher after penicillin therapy than before, while the average of the cases with successful results was unchanged. In the first 20 cases there were 14 instances in which an elevated or rising leukocyte count was followed
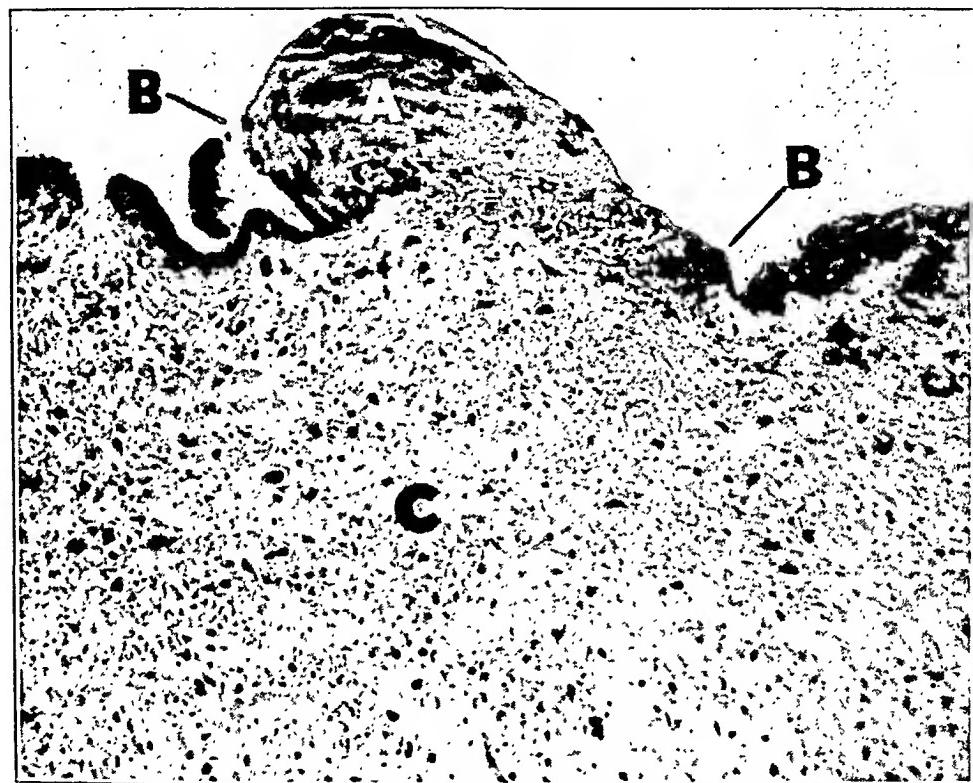
Fig. 8—Section of mitral valve of patient in case 12. *A*, thin layer of organizing fibrin free of bacteria. *B*, proliferating endocardium. *C*, organized and organizing scar tissue. × 60.

by or coincided with cultures of the blood yielding organisms. In addition, there were 2 instances in which a rising leukocyte count as an indication of activity was proved by the findings at autopsy. Less frequently occurring, but of significance is the fact that a normal leukocyte count may be obtained in the presence of a culture of the blood yielding pathogens and histologic evidence of activity. While we cannot conclude that a normal leukocyte count is an indication that all is well, we do believe that, unless explained by some complicating factor, a persistently elevated leukocyte count or a steadily rising one during treatment is a reliable indication that dosage is inadequate or that treatment should

be continued further or both. If after treatment has been stopped the leukocyte count rises steadily, we consider this a definite warning, and if coincidentally the sedimentation rate rises immediate further treatment, and, generally speaking, with considerably larger daily doses, is imperative.

In these same 20 cases there were 19 instances in which a sedimentation rate of 20 or over (Wintrobe and Westergreen) coincided with activity, as proved by either cultures of the blood which produced organisms or the postmortem finding of bacteria-filled fibrin on the valves. There were 8 instances in which a steadily rising sedi-
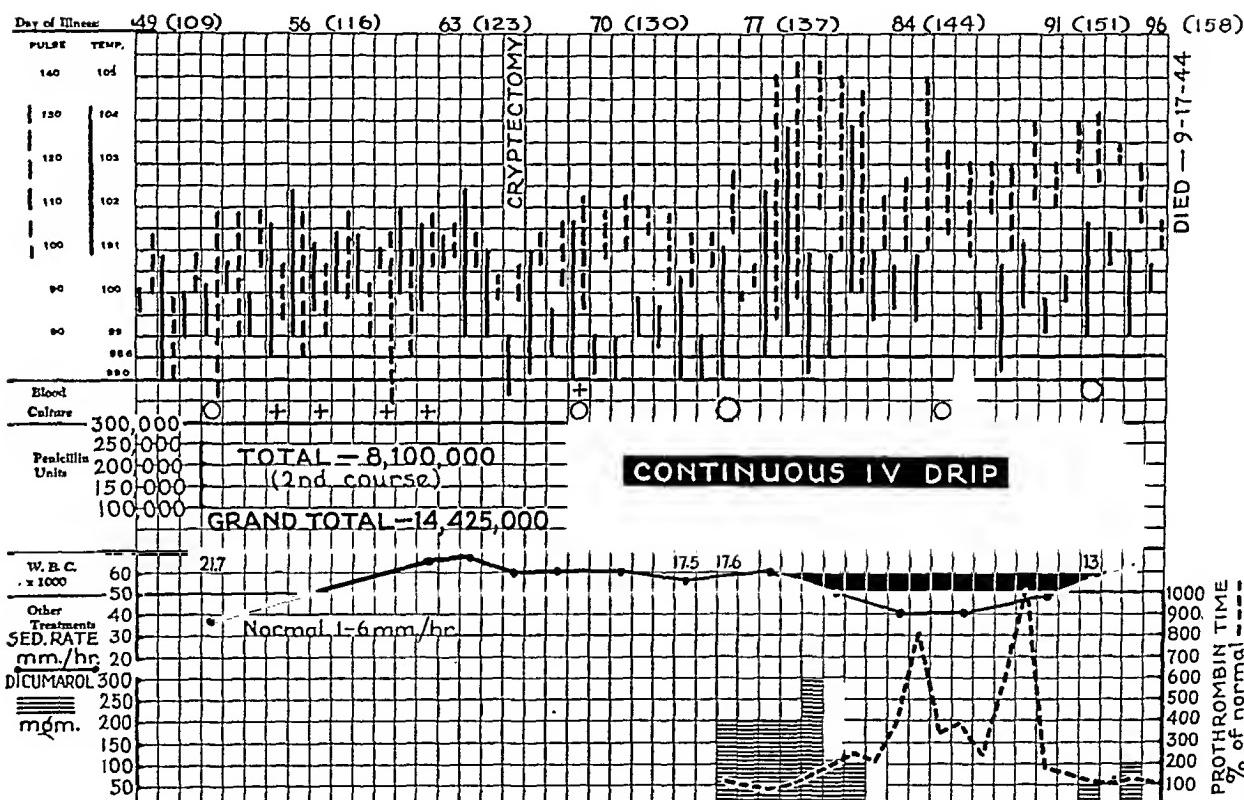
Fig. 9 (case 9).—H. P., aged 65 years, had subacute bacterial endocarditis caused by Str. viridans having a sensitivity to penicillin of 0.08 unit per cubic centimeter. Figures in parentheses indicate the approximate day of illness.

mentation rate, either during or after treatment, preceded the reappearance of pathogens in cultures of the blood or death, after which active lesions containing bacteria were found. The rise was from a normal level in 4 instances and from an elevated level in 4. All our recovered patients had normal or nearly normal sedimentation rates on discharge from the hospital or else had slightly elevated rates which steadily declined to normal over a period of a few weeks after discharge. The only exception to this in all our patients so far has been one who, although free of evidence of endocardial infection eight months after com-

pletion of therapy, has rheumatoid arthritis. Histologic proof of the relationship between a sedimentation rate which steadily declines to normal and healing of the lesion is afforded by case 12 (fig. 5). In this case the organizing process was virtually complete, the integrity of the endocardium was almost reestablished and only scattered microscopic

Fig. 10.—Section from an active lesion of the mitral valve of the patient in case 9. *A*, fibrin. *B*, clumps of cocci on the surface of and buried deeply in the fibrin. *C*, organizing scar tissue. × 60.

areas of bacteria-free fibrin were found (fig. 6). Death was due to congestive cardiac failure. Histologic proof of the relationship between leukocytosis and persistently elevated and rising sedimentation rate and an active bacteria-laden lesion, in spite of sterile cultures of the blood, is illustrated in figures 7 and 8. All patients showing active lesions at

autopsy had elevated sedimentation rates at the time of death. If we accept a sedimentation rate of 20 or over as indicating activity before therapy, it is illogical not to accept the same interpretation after therapy. At this point the elevation may mean only the persistence of fibrin or inflammatory reaction and not necessarily bacteria. But it is our conviction that until the sedimentation rate returns to normal these patients cannot be considered out of danger, and cultures of the blood, leukocyte counts and determinations of the sedimentation rate must be made at frequent intervals. These observations were confirmed in 14 of the subsequent cases.

After trying various methods for determining the sedimentation rate, we adopted that of Wintrobe, which permits of ready correction for the hematocrit reading.

SUMMARY AND CONCLUSIONS

The end results in 34 unselected cases of subacute bacterial endocarditis in which the patients were treated with penicillin are reported. Twenty-two (65 per cent) are alive and free of any evidence of the disease from thirteen to thirty-five months after completion of treatment.

Duration of the disease ranged from one and a half to fifty-two weeks before admission to our service.

Str. viridans predominated as the offending organism, but six other organisms were encountered. In vitro sensitivity of the organisms in 27 cases ranged from 0.02 to 6.0 units per cubic centimeter.

Administration of penicillin in isotonic solution of sodium chloride by continuous intravenous drip was found superior to intermittent intramuscular injection, in the maintenance both of constant adequate blood levels and of the patient's comfort. Five per cent dextrose in isotonic solution of sodium chloride was found much more likely to produce troublesome venous irritation and thrombosis.

Restriction of the intake of fluids to 800 or 900 cc. during the waking period resulted in less wide fluctuation of the serum penicillin level.

To increase the dose of penicillin seems simpler to us than to use para-aminohippuric acid or diodrast to retard the rate of excretion from the kidneys.

No clinical or histologic evidence was found to favor the use of anticoagulants. The danger of fatal hemorrhage suggests caution in their use.

Success of treatment was judged by clinical, laboratory and histologic evidence.

Adequate daily dosage over a sufficiently long period is the most important single factor in success of treatment. With the use of continuous intravenous drip, the minimal safely efficacious dose is 500.000

units per day, with administration of 1,000,000 to 2,000,000 units per day or more if clinical criteria dictate or if the disease is of over twelve weeks' duration. Daily dosage of 500,000 or more units at the outset has resulted in recovery of 100 per cent of 16 consecutive patients, as compared with 59 per cent (adjusted figures) in the first 20 patients, in which 7 of the 10 deaths occurred in patients receiving 400,000 units or less. If intermittent intramuscular injection is the only feasible method, minimal doses of 100,000 units at ninety minute intervals are recommended. Treatment should be continued for not less than four weeks.

Conclusive evidence, either in vitro or clinical, of the synergistic effect of the sulfonamide drugs was found in only 1 patient. The organism belonged to the parainfluenzal group.

In vitro sensitivity of the organism has little bearing on the outcome but is a rough guide as to the daily dose. A minimal daily dose of 1,000,000 units or more is recommended when one is dealing with organisms sensitive to only 0.1 unit or more in vitro. The possibility of the presence of a strain of Str. viridans particularly resistant in vivo should be considered as a cause of failure not otherwise explainable. A minimal daily dose of 2,000,000 units for this organism seems essential.

The most reliable indexes of successful therapy and adequacy of therapy were found to be the leukocyte count and the sedimentation rate. Sterile cultures of the blood cannot alone be considered conclusive, as they do not indicate control of the valvular lesions. These points, as well as daily dosage, in relation to the findings at autopsy will be discussed in detail in a subsequent publication.

All recovered patients were observed (blood cell counts, sedimentation rates, cultures of the blood and physical conditions) at weekly intervals during the first month after discharge, thereafter semimonthly for six months and then monthly to date.

Correspondence

To the Editor:—Readers of the article entitled "Association of Pneumonia with Erythema Multiforme Exudativum," published by the Commission on Acute Respiratory Diseases in the ARCHIVES (78:687 [Dec.] 1946), may be confused by the failure of the authors to distinguish the syndrome which they describe from another with a similar name but quite·different clinical characteristics. Osler, some fifty-two years ago, published a paper (*Am. J. M. Sc.* **110**:629 [Dec.] 1895) entitled "On the Visceral Complications of Erythema Exudativum Multiforme," in which he described 11 cases of a polymorphic syndrome which included a variety of cutaneous and visceral lesions. This clinical picture was distinctly different from that described in your journal.

In Osler's cases hemorrhagic lesions of the skin and the mucous membranes were outstanding, although cutaneous involvement also included erythema, edema and urticaria. Visceral manifestations included gastrointestinal crises, nephritis, pericarditis, possible endocarditis, splenomegaly and "bronchitis." Articular and periarticular swelling also occurred. If studied under modern conditions some of Osler's cases would probably be classified as anaphylactic purpura, acute idiopathic purpura with thrombopenia, rheumatic purpura, acute polyarteritis nodosa, acute disseminated lupus erythematosus, etc.

It seems clear that Osler and the Commission on Acute Respiratory Diseases were not describing the same syndrome, despite the similarity of terminology, and it is hoped that confusion will be a little less confounded as a result of this minor animadversion.

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News and Comment

American Society for Research in Psychosomatic Problems.—The Fourth Annual Meeting of the American Society for Research in Psychosomatic Problems will be held May 3 and 4, 1947 at Haddon Hall, Atlantic City. Dr. James L. Halliday, of Scotland, whose research in psychosomatic medicine is well known, will be one of the guest speakers. The following papers will be presented on Saturday, May 3:

The Role of Somatic Trigger Areas in the Mechanism of Certain Projection Phenomena of Hysteria. Dr. Janet Travell and Dr. Nolton H. Bigelow

Psychodynamics of Parkinsonism. Dr. Gotthard Booth

Preliminary Report on a Psychosomatic Study of Rheumatoid Arthritis. Dr. Adelaide Johnson

Psychosomatic Medicine and the Problem of Rheumatism. Dr. James L. Halliday

Studies of Syncope: IV. Biological Interpretation og Vasodepressor Syncope. Dr. George L. Engel and Dr. John Romano

The Necessity for Reorientation in Medical Education from the Psychosomatic Point of View: The Medical Curriculum, Dr. Charles Aring; Undergraduate Training. Dr. Thomas A. C. Rennie

Psychosomatic Medicine and Problems of Society. Dr. James L. Halliday

Sound Motion Picture Presentation óf a Case of Multiple Dissociation of the Personality. Dr. John G. Lynn IV and Dr. Raymond Sobel

Novel Panoramas in Psychosomatic Medicine. Dr. Bertram D. Lewin

On Sunday there will be a panel discussion, "A Survey of Several Psychodiagnostic Methods," in which Dr. Elizabeth Hellersberg, Dr. Max Hutt, Dr. Caren Machover and Dr. Bela Mittelman will participate.

Room reservations may be made directly through the hotel or the American Society for Research in Psychosomatic Problems, but dinner reservations must be made through the Society's office at 714 Madison Avenue, New York 21, New York.

American Academy of Allergy.—The American Academy of Allergy, in cooperation with the Medical Faculty of the University of California, will offer an orientation course in clinical allergy for general practitioners at the University of California Hospital, San Francisco, from July 7 to July 11 inclusive, under the auspices of Medical Extension, University of California. This course has received the approval of the Committee on Education of the American Academy of Allergy.

Book Reviews

Las neuro-bartonelosis: Sindromes neuropsiquicos de la entermedad de Carriôn—verruga peruana. By Juan B. Lastres, M.D. Price, unknown. Pp. 161. Lima, Peru: Editora medica peruana, S. A., 1945.

With the term "neurobartonellosis" the author classifies the neuropsychic syndromes of Carrion's disease which in their various forms constitute the integral part of its clinical picture. This interesting and important disease is ably and logically discussed with the help of numerous case studies compiled from the literature and from the author's experience and represents many years of observations.

A complete historical outline constitutes the initial chapter of the monograph. In sequence the scientific milestones which have led to the present day status of knowledge on the subject of Carrion's disease are reviewed. In the following chapter the author presents a thorough discussion on the pathologic anatomy of the disease. The characteristic pathologic lesions are adequately described, and an excellent series of photomicrographs is used to illustrate the micropathologic features. Following immediately is the classification and description of the various symptomatic and syndromic clinical pictures which constitute neurobartonellosis. The author's classification successfully individualizes the different neuropsychic syndromes from the maze of nervous symptoms which characterizes the disease. The next two chapters discuss in succession the effects of the disease on the vegetative nervous system, on the endocrine system and on the physicochemical, cytologic and serologic characteristics of the spinal fluid. An important discussion follows on the causation and pathologic changes of the disease, strong emphasis being laid on their relationship to the onset and course of the neuropsychic syndromes. In this section the author presents and substantiates his concept of a circumstantial affinity of the Bartonella bacilliformis for nerve elements as opposed to the theoretic existence of a neurotropic Bartonella. In the final chapters the factors involved in the diagnosis, the prognosis and the treatment of neurobartonellosis are discussed with special reference to the latest advancements made in these fields.

Dr. Lastres makes use of an extensive bibliography, which is readily obtainable from the monograph if further investigation is desired. His work is an authoritative source of reference and information and adequately covers a subject which has been largely neglected up to the present time in the study of Carrion's disease.

Agnosia, Apraxia, Aphasia: Their Value in Cerebral Localization. By J. M. Nielsen, M.D. Second edition. Price, $5. Pp. 292, with 59 illustrations. New York: Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 1946.

This monograph is a significant enlargement of the author's first edition of 1936. The chief additions consist of new and greatly expanded evidence for the author's formulations. This evidence is presented in a long chapter, which constitutes almost two thirds of the book. In an appendix a proposed new nomenclature is offered, differing from the old terminology chiefly in the frequent addition of an anatomic adjective to indicate the location of the lesion in each type of disturbance. An index greatly increases the usefulness of the book for reference.

If this, the most modern American treatise on the subject, fails of complete clarity, it is not so much the fault of the author, who has devoted tireless energy to his task, as of the complexity of the material. When agnosia, apraxia and aphasia are thoroughly understood, and their psychologic, physiologic and anatomic correlations are adequately known, the clinical application will remain surpassingly arduous because of the tedious study necessary in each case. It is to the author's

great credit that his efforts have materially advanced our knowledge and that this compact book offers so thorough a treatise in so difficult a field.

Preoperative and Postoperative Treatment. Edited by Lieut. Col. Robert L. Mason and Harold A. Zintel, M.D. Second edition. Price, $7. Pp. 584, with 157 illustrations. Philadelphia: W. B. Saunders Company, 1946.

The second edition of this book follows the first edition after a period of nine years. The contributing authors are Robert H. Aldrich, G. Kenneth Coonse, Laurence B. Ellis, E. Parker Hayden, Robert M. Kark, Donald King, Robert R. Linton, Robert L. Mason, Leland S. McKittrich, Louis E. Phaneuf, George C. Prather, Lyman Richards, Dwight L. Siscoe, Judson A. Smith, Alexander W. Souter, John W. Strieder, Arthur L. Watkins, Walter R. Wegner, Sidney C. Wiggin and Harold A. Zintel.

Almost all phases of preoperative and postoperative treatment are covered. The presentation is based both on the experience of the authors and on their review of pertinent literature. In addition to the general considerations concerning preparation of the patient in whose case the risk will be slight, other factors of age and operative risk are covered. Special attention is given to various disorders, such as nutritional diseases, cardiac disease, hypertension and nephritis and diabetes. The question of anesthesia is well considered not only in the chapter bearing that title but at intervals during discussions of other subjects. Postoperative care after the uncomplicated abdominal operation is given a good deal of attention as well as the subjects of shock, water balance, blood transfusion and acidosis and alkalosis. Care of the wound is discussed and also postoperative pulmonary complications, as well as complications of the urinary tract and venous thrombosis. There are chapters on superficial burns and on physical medicine in surgical practice. All these constitute part I of the book.

In part II the preoperative and postoperative care of patients is considered with respect to operations on various anatomic divisions of the body. Chapters deal with the ear, nose and throat, hyperthyroidism, thoracic operations, gallbladder and biliary tract, stomach and duodenum, appendix, gynecologic operations, operations on the colon and rectum and urologic surgery. A final chapter on traumatic injuries includes consideration of first aid. A valuable appendix, giving laboratory findings in blood and urine in health and disease, is included. The book is well indexed and is a valuable addition to the medical library of any practicing physician.

Undersøgelser af insulinets virkning: specielt paa blodsukkeret og det respiratoriske stofskifte ved kulhydratrig og kulhydratfattig kost. By Knud Lundboek. Pp. 209. Copenhagen: Ejnar Munksgaard, 1943.

The reviewer of this book is handicapped because his lack of reading knowledge of the Danish language limits his consideration of the monograph to its accompanying English summary and to a study of the charts and graphs.

Reported are observations on the effect of larger and smaller doses of insulin on a group of psychiatric patients given insulin for inducing hypoglycemic shock. The author regards these subjects as normal from the standpoint of metabolism and therefore considers that his observations are of general significance. They cover especially the effect of insulin and the induced hypoglycemia on the respiratory quotient with the subject subsisting on diets either high in carbohydrate (512 Gm.) or relatively low in carbohydrate (135 Gm.). He concludes that insulin inhibits hepatic glycogenolysis and that a diet poor in carbohydrate diminishes this inhibition.

Also considered are the changes effected by insulin in production of heat, respiration, ventilation and the p_H of the blood.

The author regards the respiration in profound hypoglycemia as characteristic of this state of metabolism, as much so as Kussmaul's respiration is characteristic of diabetic acidosis. The respiration is marked by changing depths of respiration, irregular jerky expirations and pauses after each phase of the respiratory cycle.

Anesthesia in General Practice. By S. C. Cullen, M.D. Price, $3.50. Pp. 260, with illustrations. Chicago: The Year Book Publishers, Inc., 1946.

This finely printed and well illustrated little book covers in a thorough manner the entire subject of anesthesia—inhalation, spinal, regional, etc. The fundamental preliminaries are adequately discussed as well as complications and sequelae. The illustrations are numerous, well selected and well reproduced, but in the reviewer's mind nothing is added by the introduction of a number of childish, if harmless, cartoons to illustrate the dire effects of certain incorrect procedures.

Tumores broncogénicos. By Dr. Hernán D. Aguilar. Pp. 438. Buenos Aires, Argentina: El Ateneo, 1946.

The author's aim in writing this book was to provide a guide to physicians of the Argentine who are interested in the study of thoracic diseases and who desire to visit medical centers concerned with their treatment in the United States. With this purpose in mind, a section of the book is devoted to a review of bronchogenic tumors, clinical material acquired by Dr. Aguilar at the Barnes Hospital. The second, and last, section of the book is dedicated to observations on the general aspects of thoracic surgery in the United States, as interpreted by the author during his stay in this country.

The pathologic physiology, the diagnosis and the anatomicophysiologic basis of the surgical treatment of bronchogenic malignant growths are extensively discussed in the preliminary chapters of the first section. A clinical and surgical survey of 264 cases, with fifty-two pneumonectomies, is presented as the nucleus of this discussion of bronchogenic tumors. Also discussed are the concept of mixed pulmonary tumors and the technic of pneumonectomy, including its complications and their treatment.

In the second section the author takes up the teaching of thoracic surgery in American medical schools and hospitals. The organization of medical and surgical services for thoracic treatment in American medical centers is described, and a chapter is devoted to a description of sanatoriums for patients with tuberculosis in this country.

The book's two subjects are totally unrelated except in their common purpose. It is felt that this end is satisfactorily achieved, and the book should be of great value to the group of physicians for whom it has been written. A comprehensive bibliography is included.

Renal Diseases. By E. J. Bell, M.D. Price, $7. Pp. 434, with 119 illustrations. Philadelphia: Lea & Febiger, 1946.

Dr. Bell's work on renal disease is too well known to require much comment. In this finely printed book, with many figures of gross and microscopic pathologic material, Bell gives a systematic discussion of renal diseases of all sorts. While the whole subject is covered, Dr. Bell's own extensive experience lends special weight to certain sections; his intimate knowledge of the pathology of renal disease is also impressive. Comprehensive bibliographies will be found especially useful by the critical reader.

TREATMENT OF PLASMODIUM VIVAX MALARIA OF FOREIGN ORIGIN

A Comparison of Various Drugs

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IT IS THE purpose of this report to present data concerning the efficacy of various drugs in the treatment of Plasmodium vivax malaria of imported origin. Observations were made on the use of quinacrine hydrochloride (atabrine), quinine sulfate and three drugs known as SN 6911 (3-methyl-4-[4-diethylamino-1-methylbutylamino]-7-chloroquinoline), chloroquine and SN 8137 (4-[3-diethylamino-2-hydroxypropylamino]-7-chloroquinoline).[1] Data on the immediate response to therapy and minor toxic symptoms after the use of all drugs and on the rates of relapse following administration of quinacrine hydrochloride, SN 6911 and chloroquine will be presented in this paper. A separate report will be presented of laboratory studies, including plasma drug concentrations, tests of hepatic function and hematologic and urinary examinations.[2] Some of the data on the patients given quinacrine hydrochloride and quinine sulfate have been included in another report comparing these two commonly used antimalarial drugs.[3]

SUBJECTS AND METHODS

All the subjects were white soldiers who had contracted malaria in either the Pacific or the Mediterranean area and who had proved relapses while under observation at Harmon General Hospital. In some of the patients, the attacks were "delayed primary" ones, i.e., the first proved attacks of malaria since cessation of the use of suppressive quinacrine hydrochloride. Some of these men had had short bouts of fever overseas, during which either no smear of the blood was made or the result was not known. In 123 patients with malaria acquired in the Pacific area who stated that they had had no proved attacks overseas, a smear positive for organisms was obtained for the first time on an average of forty-six days (standard deviation, thirty-three days) following the stated cessation of the use of quinacrine hydrochloride. The range was from six to two hundred and twenty-five days.[4] In the majority of patients, however, the relapse at this hospital was a recurrence of previously proved malaria. The number of previous attacks, according to the patients' histories, varied from one to nineteen.

No patient was treated unless a smear of his blood was positive for P. vivax and his oral temperature exceeded 100 F. Specific treatment with drugs was always started at 9 a. m. and was given according to the schedules presented here, which, for local convenience, had been modified slightly from the directed protocols. Treatment was postponed on the average for two days after the patient's admission to the treatment ward, because of other studies.[5] Fluids were forced in all patients and sedatives used as necessary. No antipyretics were used. Records were made daily of the incidence of symptoms both before and after beginning of therapy.

The density of parasites was determined in a thin smear taken just before treatment was begun. Smears were then made every twelve hours for five days.

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3. Gordon, H. H.; Christianson, H. B., and Lippincott, S. W.: A Comparison of Quinine and Quinacrine in the Treatment of the Clinical Attacks of Vivax Malaria, South. M. J. **39**:631 (Aug.) 1946.

4. In the studies at Harmon General Hospital which established the Chesson strain of P. vivax (Ehrman, F. G.; Ellis, J. M., and Young, M. D.: Plasmodium Vivax Chesson Strain, Science **101**:377 [April 13] 1945), the intervals from cessation of the use of quinacrine hydrochloride to the appearance of the first smear yielding organisms averaged thirty-two days. These studies were carried out in conjunction with the members of the United States Public Health Service according to a protocol supplied by the Board for Coordination of Malarial Studies. Five patients with neurosyphilis volunteered for the observations. They were given 0.8 Gm. of quinacrine hydrochloride on the first day and then 0.1 Gm. daily for a total of twenty-four days of medication. On the fifth day, when their plasma levels of quinacrine hydrochloride were 16 to 24 micrograms per liter, they were bitten by mosquitoes previously infected from one of our patients who had contracted malaria in New Guinea. Use of quinacrine hydrochloride was then continued for nineteen days, during which time their plasma concentrations varied from 18 to 40 micrograms per liter. Malaria developed in all 5 patients within twenty-five to forty-one days after cessation of use of quinacrine hydrochloride (Malaria Report no. 273 of the Board for Coordination of Malarial Studies from Harmon General Hospital through the Medicine Division, Office of the Surgeon General, Washington, D. C.).

5. Engstrom, W. W.; Gordon, H. H.; Marble, A., and Brunsting, H. A.: Induced Malaria of Foreign Origin, Arch. Int. Med. **79**:185 (Feb.) 1947.

Since it was found that the various drugs in the dosage used produced smears which once sterile remained so, during the latter part of the study the making of smears was discontinued after two sterile ones had been obtained. The single exception was in patients given quinine sulfate; in them, smears were obtained every twelve hours for five or seven days.

On the completion of treatment, the patients were sent to the reconditioning section or other wards of the hospital, whence they reported to the laboratory twice weekly for smears. Smears were examined on the day they were made, and if malarial parasites were found the patient was again transferred to the treatment ward. A follow-up for an arbitrary period of one hundred and twenty days was established in order to determine the rates of relapse. This seemed a reasonable procedure, since previous studies of patients with P. vivax malaria acquired in the Pacific area treated with quinacrine hydrochloride had shown that approximately 90 per cent of the observed relapses took place within one hundred and twenty days after completion of treatment and that extension of the average period of observation to one hundred and forty-three days added few relapses.[6] Although there is evidence to suggest that this may not be true for P. vivax malaria acquired in the Mediterranean area,[7] the data permit comparison of the results following use of the different drugs. The length of the period of observation of nonrelapsers is an important consideration in any discussion of "rates" of relapse.

Some patients were discharged prior to completion of the desired period of observation for administrative reasons; this has been noted in the tables to be presented. Because of the length of the study and occasionally because of the need of other sections in the hospital for beds, patients were given furloughs, usually immediately after completion of treatment. In such instances they were carefully instructed to report to an army hospital for treatment of malarial attacks. In almost all instances, smears positive for organisms were obtained before treatment; a written report of a positive smear was obtained before the relapse was considered a proved one. No attempt was made to determine the rates of relapse following administration of SN 8137 or quinine sulfate.

The dosages of the various drugs and the times of administration are given in table 1. The schedules were set up by the Board for the Coordination of Malarial Studies on the basis of preliminary reports of efficacy and toxicity supplied by both civilian and governmental sources. The protocols permitted the comparison of the effects of (a) two different salts, the bisulfate and dinaphthoate, of SN 6911 with quinacrine hydrochloride given in amounts approximating that routinely used in the Army; (b) different amounts of chloroquine with each other and with similar dosages of quinacrine hydrochloride over periods of one to six days, and (c) all drugs, with quinine sulfate in customary amounts.

All the schedules except one were based on the principle of giving relatively large doses for priming on the first day.[8] With the exception of the patients on

6. Gordon, H. H.; Marble, A.; Lippincott, S. W.; Hesselbrock, W. B., and Ellerbrook, L. D.: Clinical and Laboratory Studies of Relapsing Vivax Malaria of Pacific Origin, New England J. Med. **234**:519 (April 18) 1946.

7. Interim Report on Malaria Relapses After Treatment with Quinine and Synthetic Quinine Substitutes, Malaria Report 377, Board for the Coordination of Malarial Studies, Directorate of Biological Research, Great Britain War Office, London; personal communication to the authors.

8. Shannon, J. A.; Earle, D. P.; Brodie, B. B.; Taggart, J. V., and Berliner, R. W.: The Pharmacological Basis of the Rational Use of Atabrine in the Treatment of Malaria, J. Pharmacol. & Exper. Therap. **81**:307 (Aug.) 1944.

found between the responses to the two salts of SN 6911. Furthermore, the different doses of chloroquine led to no differences in rates of disappearance of parasites. The results for the five drugs have been summarized in chart 1.

It is seen that at twenty-four hours only 9 per cent of the smears were sterile in the patients given quinine sulfate, as compared with 37 per cent in those given SN 6911 and 48, 53 and 66 per cent in those given SN 8137, quinacrine hydrochloride and chloroquine respectively. By forty-eight hours, use of quinine sulfate had produced only 50 per cent of sterile smears as compared with 92 to 98 per cent for the four other drugs. There can be no question that quinine sulfate is inferior

TABLE 3.—*Rate of Disappearance of Parasites and Percentage of Smears Found Sterile*

Hours After Treatment	Quinine Sulfate	Quinacrine Hydrochloride				SN 6911			Chloroquine					SN 8137
		3.2	2.6	1.2	Total	N	S	Total	2.0	0.8	1.0	1.2	Total	
12...................	3	18	6	26	17	6	18	12	14	27	27	17	23	8
24...................	9	55	29	76	53	38	37	37	54	74	68	64	66	48
36...................	23	88	78	94	87	66	76	71	82	96	91	86	90	84
48...................	59	99	88	100	95	88	96	92	97	100	97	96	98	95
60...................	71	99	92	100	97	90	100	95	98	100	100	98	99	100
72...................	80	100	96	..	99	92	100	96	100	..	100	98	99	100
84...................	86	100	96	..	99	..	..	..	100	..	..	100	100	...
96...................	96	..	96	..	99	98	..	99	..	..	..	100	100	...
120...................	100	..	100	..	100	100	..	100	..	..	..	..	..	...
Number of patients....	55	40	51	50	141	50	49	99	63	55	66	51	235	63
Percentage with density. over 5,000/c.mm.	30	13	35	21	22	26	29	27	23	19	28	29	24	36

in this regard to the four other drugs tested; whether chloroquine is superior to the other three drugs in clearing the blood of parasites cannot be stated with certainty, because of the fluctuations found in the different subgroups (table 3). These fluctuations may be a reflection of the variations in distribution of densities before treatment (table 2); these in turn may be partial reflections of mechanisms of humoral immunity, which also affect the rate of disappearance of the parasites from the blood.[10] Preliminary analyses have indicated a lack of relationship between plasma levels attained and the rate of disappearance of parasites in these patients, who were given amounts of drugs probably well above the minimum amounts needed to control symptoms. The details will be presented in a separate report.[2]

10. Taliaferro, W. H., and Taliaferro, L. G.: (*a*) Active and Passive Immunity in Chickens Against Plasmodium Lophurae, J. Infect. Dis. **66**:153, 1940; (*b*) The Effect of Immunity on the Asexual Reproduction of Plasmodium Brasilianum, ibid. **75**:1, 1944.

Subsidence of Fever.—Although the synthetic drugs were superior to quinine sulfate in ridding the blood of parasites, all drugs were effective in controlling fever.   It is seen that from 71 to 91 per cent of the patients had normal temperatures on the day beginning twenty-four hours after treatment was started.   The lowest percentage of normal temperatures on the first day after treatment, 71 per cent, was obtained in the patients given SN 8137.   This was associated with the highest incidence of patients who had a rise in temperature on the day treatment was begun, with the fever continuing into the next day.   No ready explanation of this is at hand.   It may have been due to some specific pyrogenic effect of the drug or to the chance inclusion in this small group of a larger percentage of patients who would have had another paroxysm on the day treatment was begun.   Opportunities were not available to study this point.

TABLE 4.—*Time of Subsidence of Fever*

Drug	Number of Patients	Percentage of Patients with Normal Temperature, i. e., Less Than 100 F. on Day Beginning 24, 48 and 72 Hr. After Treatment Was Begun		
		24 Hr.	48 Hr.	72 Hr.
Quinine sulfate	56	78	100	100
Quinacrine hydrochloride	141	91	99	100
SN 6911	99	88	97	99
Chloroquine	236	90	100	100
SN 8137	63	71	100	100

Although no significant differences in the rate of disappearance of parasitemia or fever were found in the subgroups, the clinical impression was obtained that the patients given the smallest dose of quinacrine hydrochloride (1.2 Gm. per day) and chloroquine (0.8 Gm. for six days) continued to feel under par a little longer than those given larger amounts of the drugs.   It is also of interest that 1.2 Gm. of quinacrine hydrochloride controlled the fever and parasitemia so well, since the previous disrepute of quinacrine hydrochloride for immediate control of fever and parasitemia was derived from experience with 1.5 Gm. of the drug.[11]   The difference is probably accounted for by the fact that in our observations 1.2 Gm. was given in one day, whereas in the discarded schedule only 0.3 Gm. daily for five days was given.   The importance of quickly building up plasma concentrations of quinacrine hydrochloride has been demonstrated by Shannon and his co-workers.[8]   Evidence will be presented in a separate report that satisfactory concentrations were attained in the present study.[2]   No attempts were made to determine the interval until relapse after the one day treatment with

11. Napier, L. E.: The Present Status of Antimalarial Drugs, New England J. Med. **233**:38 (July 12) 1945.

quinacrine hydrochloride. It has already been pointed out that these patients did not feel so well as those given customary doses of quinacrine hydrochloride, and this one day schedule is not suggested as a substitute for the customary schedule of 2.8 Gm. in seven days, which is supported by a wealth of experience.[12]

Minor Toxic Symptoms.—The incidence of minor toxic symptoms is presented in table 5. No symptom was considered attributable to therapy unless it was first noted on the second day of treatment. This criterion seemed desirable in order to avoid confusing minor toxic symptoms resulting from therapy with those of malaria. It is seen that, in general, more minor toxic symptoms followed the administration of

TABLE 5.—*Number of Patients with Minor Toxic Symptoms Attributed to Therapy During Malarial Relapse*

	Drug				
	Quinine Sulfate	Quinacrine Hydrochloride	SN 6911	Chloroquine	SN 8137
Number of patients............	55	137	82	236	63
Symptoms *					
Nausea....................	8	2	5	8	1
Vomiting.................	0	2	3	2	1
Anorexia.................	22	2	†	10¶	1
Diarrhea.................	8	6	6	8	5#
Abdominal cramps........	†	†	†	4	1
Dizziness.................	12	0	0	2	4
Tinnitus.................	35	0	2	0	2
Diminished hearing.......	8	0	†	0	0
Blurring of vision........	†	†	†	0	2
Pruritus.................	3	0‡	†	17	4
Urticaria.................	0	0	0	2	1
Rash.......	1	†§	0	?1	1

* No symptom was attributed to therapy unless it was first noted on the day after treatment was begun.

† Records were inadequate for tabulation.

‡ Pruritus was observed in 7 patients not in this series, but all of them had diseases of the skin.

§ Rash occurred in 6 patients not in this series; some of them had active dermatitis.

¶ Both the largest (2.0 Gm.) and the smallest (0.8 Gm.) doses of chloroquine were associated with anorexia in 5 patients each; with the intermediate doses of 1.0 and 1.2 Gm. this was not noted.

Diarrhea, which appeared attributable to the drug, occurred suddenly in 5 patients on the first day of treatment.

quinine sulfate than of the synthetic drugs. Pruritus developed in 17 patients, or 7 per cent, of those given chloroquine which was not associated with rash but which produced considerable discomfort in some patients. This was seen six times in patients given 2.0 Gm. and six times in patients given only 1.2 Gm. of the drug.

12. (*a*) Dieuaide, F. R.: Clinical Malaria in Wartime, War Med. **7**:7 (Jan.) 1945. (*b*) Hudson, E. H.: Quinine and Atabrine: Development and Present Application, U. S. Nav. M. Bull. **45**:57 (July) 1945.

The newer synthetic drugs had no particular advantages over quinacrine hydrochloride with respect to toxic symptoms except that they could be given to patients who were sensitive to quinacrine hydrochloride. These were essentially of two groups. The first consisted of a number of patients from the section of dermatology who had eczematoid dermatitis or atypical lichen planus, in the causation of which quinacrine hydrochloride may have played a part.[13] Attempts to treat their malaria with quinacrine hydrochloride led to pronounced exacerbation. Treatment of some of these with chloroquine or SN 8137 controlled the malaria without deleterious effect on the disease of the skin. The second and much smaller group consisted of the rare persons in whom severe vomiting and diarrhea developed even with administration of small doses of quinacrine hydrochloride. In both of these groups in the past, quinine sulfate, which is inferior to quinacrine hydrochloride not only because of its greater incidence of production of minor toxic symptoms but because of the shorter interval until relapse,[14] would have had to be given. The case of a patient sensitive to quinacrine hydrochloride for whom one of the new synthetic drugs was a boon is illustrated in the following report of a chronic carrier of Plasmodium falciparum who was apparently successfully treated by the administration of SN 6911.

The patient, a 35 year old white soldier, was admitted to Harmon General Hospital on June 22, 1944, with a transfer diagnosis of chronic malaria due to P. falciparum. According to his past history, he had contracted malaria of unknown type while in Spain in 1936. He stated that he had had two mild recurrences in Spain in 1937 and one in California in 1939. He was inducted into the United States Army on May 15, 1942 and served in North Africa, Sicily and Italy from June 1943 until his return to the United States in January 1944. He had been in Army hospitals because of malaria on six occasions before the hospitalization, in November 1943, which led to his evacuation to the United States. Records from the hospitals accompanying the patient indicated that smears were positive for malarial parasites in November 1943, January, February, March, April, May and June 1944. During each of these months except January, when the type of parasite was not reported, the smears were repeatedly positive for P. falciparum. During this period of eight months the patient was treated with quinine sulfate, oxophenarsine hydrochloride, and quinacrine hydrochloride, although there was one note indicating that he was "unable to take quinacrine hydrochloride."

On June 29, seven days after his admission to this hospital, a smear was obtained because he complained of weakness. Although he had no fever, the smear contained gametocytes of P. falciparum. He was transferred to the treatment ward, where his temperature rose to 100.4 F., and he complained of generalized aches. On June 30, a smear was again positive for malarial parasites, this time for both P. falciparum and P. vivax. A smear taken on the morning of July 1 contained only P. vivax. At this time, he was persuaded to take quinacrine

13. Livingood, C. S., and Dieuaide, F. R.: Untoward Reactions Attributable to Atabrine, J. A. M. A. **129**:1091 (Dec. 15) 1945.

14. (a) Green, R. A.: Totaquine in the Treatment of Malaria, Bull. U. S. Army M. Dept., January 1945, no. 84, p. 51. (b) Dieuaide.[12a]

hydrochloride, although he stated that he had never been able to retain it. He was given 0.4 Gm. at 9 a. m., and at 2 p. m. he vomited brightly yellow–stained material. Administration of quinacrine hydrochloride was discontinued, and on July 2 he was started on SN 6911 dinaphthoate. The smear taken just prior to treatment was sterile, but he had a slight chill, with a rise in temperature to 101.8 F., during the early afternoon. Smears taken daily during seven days of treatment and twice weekly thereafter were sterile for the next month. On August 7 he was admitted to the treatment ward again because of a slight chill and a temperature of 100 F. His smear was positive for P. vivax. His temperature rose to 101.4 F. on the afternoon of August 7, was normal on August 8 and rose to 104.2 F. at noon of August 9. Use of SN 6911 dinaphthoate was started on the morning of August 9, with good clinical response. Smears were positive daily for P. vivax from August 7 to August 12 inclusive but remained sterile on daily examination until

TABLE 6.—*Rates of Relapse Following Treatment of "Delayed Primary" Attacks of Malaria Acquired in the Pacific Area*

Drug	Total Number of Patients	Relapsers					Nonrelapsers			
		Total Re-lapses	Sixty Day "Re-lapse Rate," %	Time Until Relapse, Days			Number	Period of Obser-vation, Days		
				Mean	Mini-mum	Maxi-mum		Mean	Mini-mum	Maxi-mum
Quinacrine hydrochloride 3.2/7 days or 2.6/6 days	22	17	77	66	30	192	5	121	86	189
SN 6911 N and S 3.2/7 days..............	13	12	92	46	29	76	1	112	..	..
Chloroquine 2.0/6 days..............	19	12	63	54	36	75	7	98	75	122
1.2/3 days..............	14	11	79	63	41	121	3	93	81	108
1.0/1 day..............	11	10	91	54	39	89	1	176	..	..
0.8/6 days..............	13	9	69	75	27	131	4	121	97	161
Total..............	57	42	74	61	27	131	15	108	75	176

August 16 and on twice weekly examinations until discharge on October 26. During this period he was admitted to the wards of the hospital from the reconditioning section on two occasions, once because of acute tonsillitis and once because of acute alcoholism; neither of these illnesses precipitated malaria.

In summary, this patient, who tolerated quinacrine hydrochloride poorly, had blood smears repeatedly positive for P. falciparum over a period of eight months. The administration of SN 6911 dinaphthoate brought his symptoms under control, and repeated smears taken over a period of four months remained negative for P. falciparum. Apparently, this drug cured this soldier of P. falciparum infection just as quinacrine hydrochloride would have done [12a] and was effective where quinacrine hydrochloride had failed because of his intolerance.

Rates of Relapse.—Rates of relapse following treatment with quinacrine hydrochloride, SN 6911 and chloroquine are presented in tables 6, 7 and 8 for patients with "delayed primary" and secondary attacks of malaria acquired in the Pacific and Mediterranean area respectively. The term "sixty day rate of relapse" has been used to indicate that no patient was considered a nonrelapser unless he had been observed for

at least sixty days following completion of treatment. As previously stated, it had been originally planned to observe all nonrelapsers for at least one hundred and twenty days. Administrative reasons, however, made this impossible in some cases. For each group of patients, there-

TABLE 7.—*Rates of Relapse Following Treatment of "Secondary" Attacks of Malaria Acquired in the Pacific Area*

| | | Relapsers | | | | | | Nonrelapsers | | |
| | | | Sixty Day "Re- lapse Rate," % | Interval to Relapse, Days | | | | Period of Obser- vation, Days | | |
Drug	Total Number of Patients	Total Re- lapses		Mean	Mini- mum	Maxi- mum	Number	Mean	Mini- mum	Maxi- mum
Quinaerine hydrochloride 3.2/7 days or 2.6/6 days	39	26	67	63	34	120	13	100	78	129
SN 6911 N and S 3.2/7 days..............	62	37	70	48	18	89	25	87	62	147
Chloroquine										
2.0/6 days..............	30	18	60	56	43	81	12	103	62	127
1.2/3 days..............	13	9	69	58	41	91	4	110	62	132
1.0/1 day..............	35	29	83	56	39	154	6	127	106	158
0.8/6 days..............	33	27	82	57	36	113	6	122	76	153
Total..............	111	83	75	57	36	154	28	113	62	158

TABLE 8.—*Rates of Relapse Following Treatment of "Secondary" Attacks of Malaria Acquired in the Mediterranean Area*

| | | Relapsers | | | | | | Nonrelapsers | | |
| | | | Sixty Day "Re- lapse Rate," % | Interval to Relapse, Days | | | | Period of Obser- vation, Days | | |
Drug	Total Number of Patients	Total Re- lapses		Mean	Mini- mum	Maxi- mum	Number	Mean	Mini- mum	Maxi- mum
Quinaerine hydrochloride 3.2/7 days or 2.6/6 days	26	15	58	69	32	108	11	128	96	141
SN 6011 N and S 3.2/7 days..............	15	14	93	56	29	101	1	183	..	..
Chloroquine										
2.0/6 days..............	12	2	17	57	43	70	10	111	69	166
1.2/3 days..............	8	5	63	54	45	72	3	101	82	132
1.0/1 day..............	14	6	43	57	38	75	8	134	119	164
0.8/6 days..............	6	4	67	54	38	74	2	138	127	148
Total..............	40	17	43	55	38	75	23	120	69	166

fore, the average period of observation of nonrelapsers has been indicated. Lengthening of this period would tend to increase the rate of relapse and also to increase the mean interval until relapse occurred.

With these qualifications in mind, it is seen in tables 6 and 7 that high rates of relapse, from 63 to 93 per cent and from 60 to 83 per cent, were found following treatment of "primary" and secondary attacks respectively of malaria acquired in the Pacific area. None of the drugs

had any superiority over the others, and the administration of different doses of chloroquine resulted in no striking differences.

It is further seen that there were no differences between the rates following "primary" and secondary attacks. Since the groups are small, however, it would not be justifiable to assume that the same results would be obtained in large organizations.

In malaria acquired in the Mediterranean area widely fluctuating results were obtained. Following the use of chloroquine the rates of relapse averaged 43 per cent, varying from 17 to 63 per cent. Following the use of quinacrine hydrochloride and SN 6911 the rates were 58 and 93 per cent. The cause for this variability is not obvious, but it may be explained by the smallness of the groups and possibly by the greater variation in the number of strains and amount of infection which the patients contracted in North Africa, Sicily and/or Italy. In a study of mosquito-induced malaria, a much lower rate of relapse was observed following delayed treatment with quinacrine hydrochloride of malaria contracted in the Mediterranean area than following the same treatment of malaria contracted in the Pacific area, suggesting an essential difference between the malaria from these two sources.[15] Further evidence for such a difference is the longer interval until a delayed primary attack of malaria contracted in the Mediterranean area (one hundred and fifty-four to one hundred and eighty-two days in 3 patients observed in this hospital and two hundred days in the patient of Cavanaugh [16]), as compared with the average of forty-six days in our patients with delayed primary attacks of malaria acquired in the Pacific area.

Intervals Until Relapse Following Treatment.—The intervals until relapse following treatment are given in table 9 for the patients with malaria acquired in the Pacific area. No data are presented on the intervals until relapse of malaria contracted in the Mediterranean area, because of the small number in each therapeutic group. It is seen that the majority of relapses took place from the fifth to the ninth week following cessation of treatment with any of these drugs. The various doses of chloroquine led to no significant differences in the time at which relapses occurred. Following the use of SN 6911, thirteen, or 27 per cent, of the observed relapses occurred during the first five weeks after treatment, as compared with only 7 per cent following the administration of quinacrine hydrochloride and 2 per cent following use of chloroquine.

15. Gordon, H. H.; Marble, A.; Engstrom, W. W.; Brunsting, H. A., and Lippincott, S. W.: Relapses Following Delayed Treatment of Naturally Induced Vivax Malaria of Pacific Origin, Science **103**:391 (March 29) 1946.

16. Cavanaugh, R. L.: Malaria Appearing After Discontinuance of Atabrine Prophylaxis, Bull. U. S. Army M. Dept., December 1944, no. 83, p. 120.

In this respect, chloroquine is apparently superior to SN 6911 as a substitute for quinacrine hydrochloride.

No attempt was made to determine the rates of relapse following the use of quinine sulfate or SN 8137. Fifteen patients treated in this hospital with quinine sulfate had proved relapses while under observation; ten of these occurred between nine and twenty days after completion of treatment. In the whole group of 217 patients with relapses following treatment with the synthetic drugs, only 1 patient had a relapse within the first three weeks. Six relapses have been seen following the use of SN 8137; these occurred within thirty-one to

TABLE 9.—*Interval Until Relapse in Malaria Acquired in the Pacific Area*

Days to Relapse	Quinacrine Hydrochloride		SN 6911		Chloroquine Total		2.0		1.2		1.0		0.8	
	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %
1-7	0	..	0	..	0	..	0	..	0	..	0	..	0	..
8-14	0	..	0	..	0	..	0	..	0	..	0	..	0	..
15-21	0	..	1	2	0	..	0	..	0	..	0	..	0	..
22-28	0	..	2	6	1	1	0	..	0	..	0	..	1	3
29-35	3	7	10	27	1	2	0	..	0	..	0	..	1	6
36-42	3	14	5	37	18	16	4	13	2	10	6	15	6	22
43-49	9	35	8	53	36	45	6	33	7	45	16	56	7	42
50-56	8	53	13	80	18	59	6	53	3	60	2	62	7	61
57-63	4	63	3	86	23	78	9	83	2	70	9	85	3	69
64-70	2	67	2	90	5	82	1	87	1	75	2	90	1	72
71-77	3	74	2	94	9	89	3	97	2	85	1	92	3	81
78-84	4	84	1	96	2	90	1	100	0	85	1	95	0	..
85-90	1	86	2	100	3	93	..	..	0	85	1	97	2	86
91-120	5	98	..	..	5	97	..	..	2	95	0	..	3	94
121-150	0	..	..	..	3	99	..	..	1	100	0	..	2	100
151-180	0	..	..	..	1	100	..	..	..	..	1	100	..	..
181-210	1	100	..	..	..	..	..	..	..	..	..	..	..	..
Total	43		49		125		30		20		39		36	

thirty-nine days following completion of treatment, indicating that relatively early relapses can occur with administration of this drug as well as of the other synthetic drugs.

COMMENT

As part of the drug-testing program of the Board for Coordination of Malarial Studies, three synthetic drugs, SN 6911, chloroquine and SN 8137, were made available for comparison with quinacrine hydrochloride in the treatment of soldiers with relapsing P. vivax malaria of foreign origin. The achievement of two main purposes was desired. The first and most important was to find a drug which would be truly curative and therefore preferable to quinacrine hydrochloride. The second was to find a drug as efficacious as quinacrine hydrochloride in

the acute attack but without minor disadvantages such as staining of the skin or major disadvantages such as unsuitability in patients with natural or acquired sensitivity to the drug.

Although significant gastrointestinal intolerance occurs only rarely, the extensive use of quinacrine hydrochloride as a suppressive agent has been associated with the development of dermatitis in a considerable number of soldiers. The actual incidence of this condition is low, but the treatment of malaria or the continued need for suppressive treatment in these soldiers is a problem because of the inferiority of quinine sulfate to quinacrine hydrochloride. All three new synthetic drugs tested proved to be satisfactory substitutes for quinacrine hydrochloride in their ability to control the acute attacks of malaria and in the low incidence of production of minor toxic symptoms when used in the doses described. Furthermore, they were well tolerated by patients who were intolerant to quinacrine hydrochloride. Several patients whose 'dermatitis showed exacerbation under treatment in this hospital with quinacrine hydrochloride took the prescribed doses of chloroquine and SN 8137 without difficulty. None of these men were given suppressive therapy over long periods with the new synthetic drugs to test the possible development of sensitivity to them. One patient who was a chronic carrier of P. falciparum for eight months was apparently cured during a four month observation period by the administration of SN 6911, just as he would have been cured had he been able to ingest and retain quinacrine hydrochloride.

The most important goal, however, complete cure, was not attained. The rates of relapse remained high in malaria contracted in the Pacific and Mediterranean areas and were not significantly different from those observed following routine treatment with quinacrine hydrochloride. As indicated, some differences were found in the intervals until relapse, relapses coming at a shorter interval following use of SN 6911 than following use of quinacrine hydrochloride or chloroquine. Presumably this is due to differences in the rate of disappearance of these antimalarial drugs from fluids in the body.

Another factor which might affect the occurrence of a relapse and the interval is the person's "immunity." This is a complex subject,[17] but, theoretically, decreases in either intracellular or extracellular factors or both might be responsible for the reappearance of parasites in the peripheral blood. Because the density of parasites just before treatment might be considered an index of immunity, an attempt was made to relate this to incidence of relapses. No such relationship was found. An attempt was then made to relate it to the interval until relapse; these

17. (a) Coggeshall, L. T.: Immunity in Malaria, Medicine **22**:87 (May) 1943. (b) Taliaferro, W. H.: Immunity in Malaria, Am. J. Clin. Path. **14**:593 (Dec.) 1944.

data are presented in chart 2 for three groups of patients treated with SN 6911 (3.2 Gm.), quinacrine hydrochloride (2.6 or 3.2 Gm.) and chloroquine (1.0 or 1.2 Gm.). It is seen that within each therapeutic
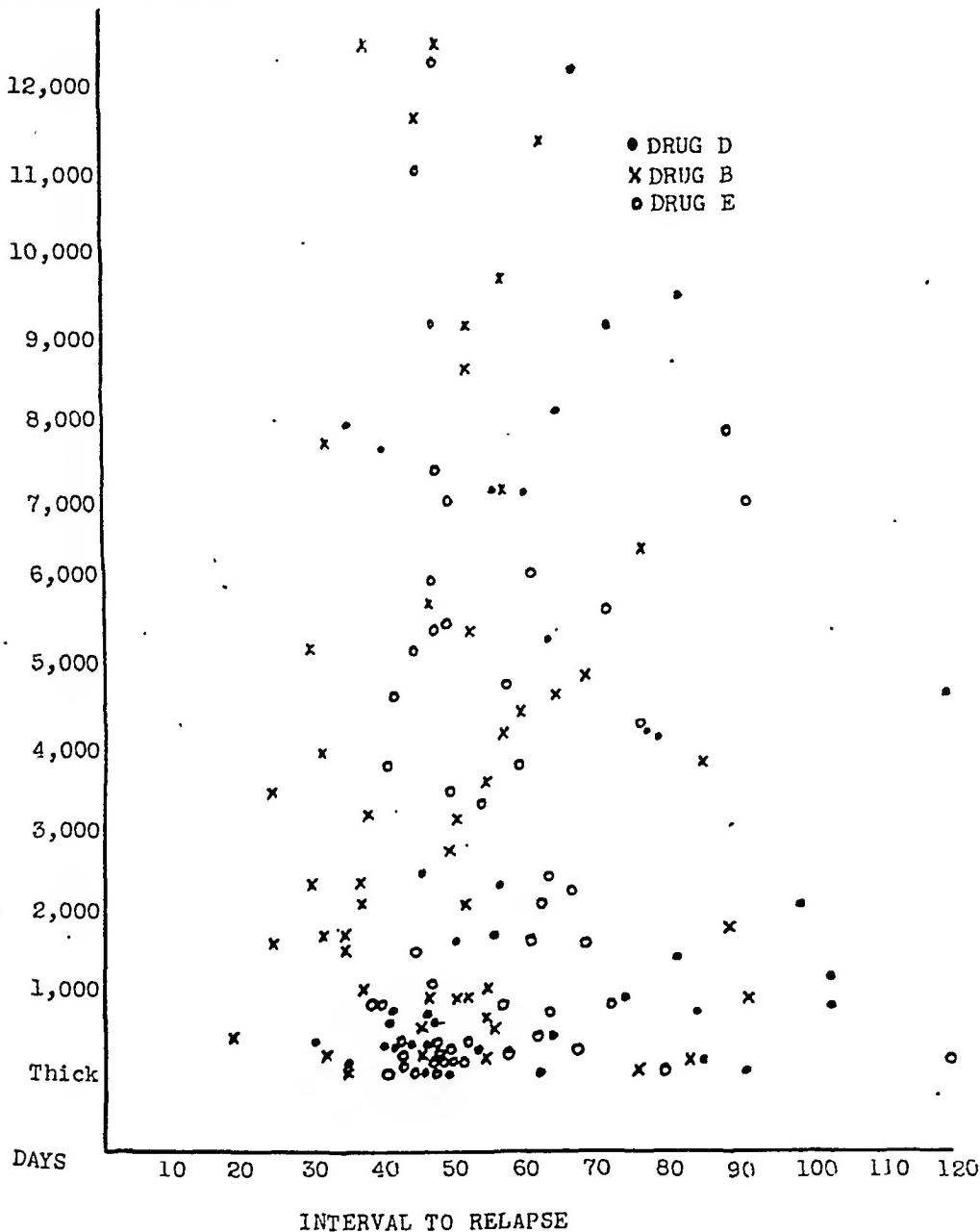
Chart 2.—Relationship of density of parasites to the time of relapse in P. vivax malaria contracted in the Pacific area. Drug B is SN 6911 (3.2 Gm. of base in seven days); drug D is quinacrine hydrochloride (3.2 or 2.6 Gm. in seven or six days), and drug E is chloroquine (1.0 or 1.2 Gm. of base in one or three days). Interval until relapse is given in days following completion of treatment.

group there was no relationship between the interval until relapse following treatment and the density of parasites just before treatment. Patients who had so few parasites that they were found in only a thick

smear relapsed in as early as forty and as late as one hundred and twenty days; patients who relapsed at fifty days had densities varying from smears which were positive for organisms only when thick to smears containing as high as 12,000 per cubic millimeter and over.

SUMMARY AND CONCLUSIONS

1. Three synthetic drugs, SN 6911, chloroquine and SN 8137, were used in the treatment of relapsing P. vivax malaria of foreign origin in doses recommended by the Board for the Coordination of Malarial Studies.

2. Neither SN 6911 nor chloroquine was more effective than quinacrine hydrochloride in curing the patients of relapses, and some evidence was collected that SN 8137 would also be ineffective. The interval until relapse in a small number of patients was shorter following use of SN 6911 than following use of chloroquine or quinacrine hydrochloride.

3. All three drugs were found to be effective in controlling the parasitemia and fever of the relapse and to cause the patient relatively few minor toxic symptoms. Because none of them stain the skin and because the widespread use of quinacrine hydrochloride has led to the development of sensitivity to the drug in a small percentage of soldiers, the drugs tested may prove of value as a substitute for quinacrine hydrochloride in therapy of the acute attack. All four synthetic drugs were superior to quinine sulfate.

COEXISTING TUBERCULOSIS AND COCCIDIOIDOMYCOSIS

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THE COEXISTENCE of active tuberculosis and coccidioidomycosis is rare. Smith[1] has reported the cases of many persons who have had positive reactions to tuberculin tests of the skin with active coccidioidal infections. He further described the similarity of physical and roentgenologic findings in the two diseases. Cherry and Bartlett[2] have recently reported a case of coexisting active tuberculosis and coccidioidal infection. Smith[3] mentioned the presence of coccidioidal infection superimposed on active tuberculosis. He described 1 patient with a tuberculous effusion on one side in whom a coccidioidal effusion developed on the other side. We present a case of a spontaneous hydropneumothorax in which were isolated both Coccidioides immitis and Mycobacterium tuberculosis.

REPORT OF A CASE

The patient is a 27 year old white soldier who entered the hospital complaining of shortness of breath on exertion. His past history revealed no significant medical or surgical diseases. In September 1943, while on duty in the desert training area of California, he first became aware of weakness, fatigue and pain in the left pleural area. He was hospitalized in a field hospital and after a short period of observation was transferred to a station hospital, where a diagnosis of coccidioidomycosis was made by roentgenologic examination and the finding of double-contoured spherules of C. immitis in the sputum. He was given complete rest in bed, and after five months he was discharged to full military duty as apparently cured. Further details of this hospitalization are not available. During the period from March 1944 to August 1944 the patient was on active duty, complaining of intermittent pain in the pleural area bilaterally which was mild and

1. Smith, C. E.: Parallelism of Coccidioidal and Tuberculous Infections, Radiology 38:643-648 (June) 1942.

2. Cherry, C. B., and Bartlett, A. G.: The Diagnosis of Acute Coccidioides Immitis Infections, Bull. U. S. Army M. Dept. 5:190-193 (Feb.) 1946.

3. Smith, C. E.: Personal communication to the authors.

nonincapacitating. Repeated physical and roentgenologic examinations of his chest during this period revealed no abnormalities. In August 1945, while in the European Theater of Operations, he began to complain of sore throat and blood-streaked sputum.. This was followed by weakness, pain in the right side of the chest and malaise. The pain in the chest was sharp in intensity and was increased by deep breathing, coughing or sudden movements. He was admitted to an overseas general hospital on Aug. 6, 1945. During this hospitalization the temperature ranged between 98.6 and 100.4 F., the pulse rate ranged from 90 to 110 and the blood pressure was 130 systolic and 84 diastolic. Roentgenologic examination revealed pronounced collapse of the right lung, with a hydropneumothorax involving the right side. The patient was given complete rest in bed. Repeated thoracenteses were performed, from 1,500 to 2,000 cc. of fluid being removed during each procedure. No expansion of the collapsed lung was noted. The fluid was straw colored, with a specific gravity range between 1.018 and 1.022. Bacteriologic examination revealed a sterile fluid. Cytologic examination revealed from 2,000 to 2,500 white blood cells, with a differential count of 75 per cent polymorphonuclear leukocytes and 25 per cent lymphocytes. Yeasts, fungi or molds were not noted on direct smear. Acid-fast stains yielded normal results. The peripheral white blood cell count varied between 10,000 to 10,500, with 60 to 65 per cent neutrophils and 35 to 40 per cent lymphocytes. The erythrocyte sedimentation rate (Westergren) varied between 15 and 18 mm. per hour. Smears were negative for malarial parasites. The patient was subsequently evacuated to the Zone of the Interior as a litter patient, with a diagnosis of hydropneumothorax involving the right side, cause unknown.

On Nov. 10, 1945 he was admitted to the Rhoads General Hospital, complaining of weakness and dyspnea on slight exertion. Physical examination revealed a well nourished white man in no apparent distress. There was no evidence of cyanosis, jaundice or edema. There was a slight shift of the trachea to the left. The thorax appeared symmetric in outline. The right hemithorax did not move with respiration. Percussion revealed dulness over the upper two thirds of the right lung, changing to flatness in the region of the lower third. Breath sounds were absent except over the paravertebral area of the right lung, where distant bronchial breath sounds were noted. Vocal egophany was notably present on the right side. The coin test gave a positive result over the upper third of the right side of the chest. Metallic tinkles were heard following inspiration, which suggested the passage of air through the fluid. The left lung was clear. Palpation revealed a slight shift of the heart to the left, but otherwise no remarkable features were noted. The remainder of the physical examination revealed no abnormalities.

Course in the Hospital.—The patient was afebrile throughout this period of hospitalization. He gained weight and noted the progressive disappearance of the exertional dyspnea. Roentgenologic studies, which are reported in detail here, revealed the presence of a collapsed right lung, with a large hydropneumothorax. Aspiration of the right side of the chest was performed on three different occasions. During the first two aspirations 1,500 cc. of cloudy yellow-brown fluid was removed. The last thoracentesis, performed six weeks later, was productive of 300 cc. of clear amber fluid. Detailed laboratory studies of the fluid are reported in succeeding paragraphs. No air was replaced after the removal of large amounts of fluid, and the lung revealed no reexpansion. This, together with the physical findings, suggested the presence of a patent bronchopleural fistula. It was felt that it was probably high in the apex, since the patient did not cough or expectorate to any degree.

Bronchoscopy was performed and revealed a normal tracheobronchial tree except for some shortening on the right side, which was to be expected in view of the collapsed right lung. Solution of methylene blue was instilled into all divisions of the right bronchus but could not be subsequently recovered in the pleural fluid.

Reaction to a coccidioidin test of the skin, in a dilution of 1 : 100, was negative on November 22 but was definitely positive when the test was repeated six weeks later. The reaction to a tuberculin test of the skin was positive in a dilution of 1 : 1,000,000.
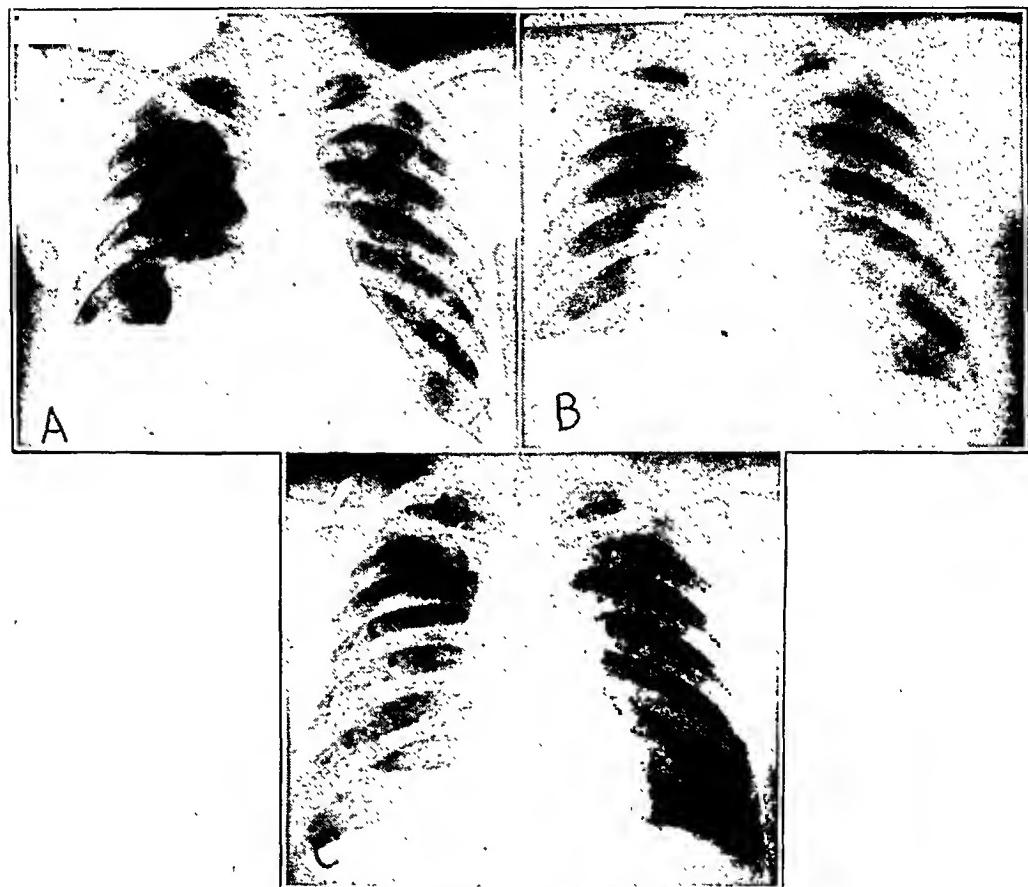
Fig. 1.—*A*, roentgenogram of the chest four weeks following the onset of the present illness. Note the extensive hydropneumothorax involving the right side and the symmetric collapse of the right lung; the arrow points to a discrete leison in the left parahilar region. *B*, roentgenogram in the fourteenth week of illness. Note the disappearance of adhesions, with almost complete collapse of the right lung. *C*, roentgenogram in the twenty-third week of illness. Note the definite reexpansion of the right lung.

The patient continued to improve during this hospitalization, but, in view of the persistent collapse of the right lung and the reasonable assumption of the existence of an open bronchopleural fistula, surgical correction was considered. However, serial roentgenologic studies revealed beginning expansion of the right lung on Dec. 29, 1945, which has since continued progressively. It is presumed that spontaneous closure of the fistula has occurred. Conservative treatment has since been continued. The patient is asymptomatic, with no evidence of disseminated lesions.

Roentgenologic Studies.—At the time of the first roentgenogram, four weeks following the onset of the present illness (fig. 1 *A*), a massive pleural effusion on the right side had been partially replaced by a pneumothorax. The right lung was collapsed symmetrically, and numerous thick adhesions crossed between the lung and the wall of the chest. A few pockets of fluid remained. For several weeks the fluid reaccumulated. Repeated drainage was performed, and no air was injected into the pleural cavity. A roentgenogram (fig. 1 *B*) in the fourteenth week of illness showed a complete collapse of the right lung, with massive pneumothorax. All adhesions had disappeared, and the collapsed lung was covered
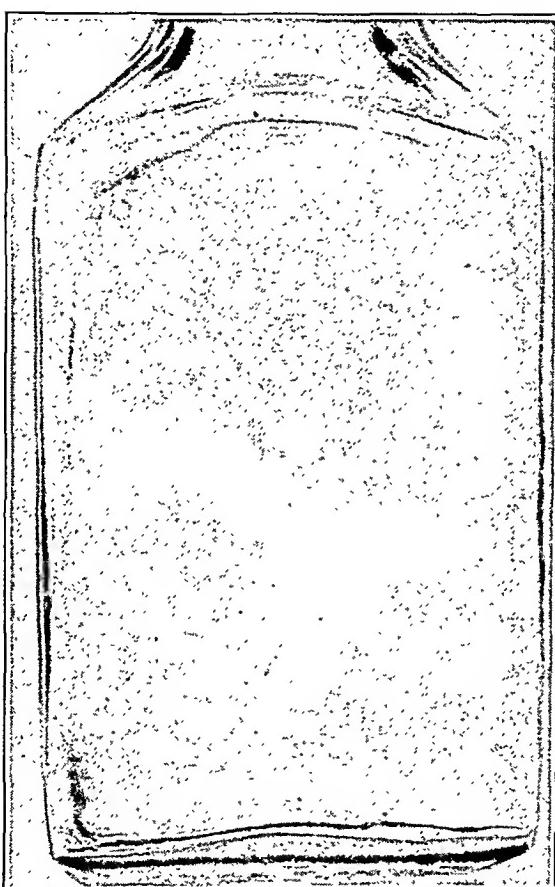
Fig. 2.—Sabouraud's maltose peptone agar medium. Note the snow white, fluffy and flakelike growth of C. immitis isolated from the pleural fluid.

by a layer of thickened pleura, varying from 5 to 20 mm. in thickness. The remaining pleural fluid was still freely movable. The right lung remained collapsed for several weeks and then slowly and evenly began to reexpand. Figure 1 *C*, taken at the twenty-third week, shows a 60 per cent reexpansion of the lung. The thickened visceral pleura had disappeared. Neither hilus was enlarged. No parenchymal infiltration was visible in the right lung.

A discrete, stationary lesion in the opposite lung (fig. 1 *A*, arrows) had been observed during the entire period of the present illness. It was firm, round and sharply defined and was in the left parenchyma close to the hilus. No cavity or calcium was observed in it. The adjacent hilus was not enlarged.

Laboratory Data.—On admission the red and white blood cell counts were 4,420,000 and 9,650 respectively, and the hemoglobin content was 94 per cent. A differential white blood cell count revealed 62 per cent neutrophils, 34 per cent lymphocytes and 4 per cent monocytes. The erythrocyte sedimentation rate (Westergren) on admission revealed an elevation to 16 mm. per hour. The initial and subsequent urinalyses revealed no abnormalities. Smears of the blood

Fig. 3.—Direct smear from a culture of C. immitis. Note the mycelial network with branching hyphae and conidia. × 980.

were persistently negative for malarial parasites. Repeated blood cell counts revealed a white blood cell count ranging between 8,500 and 9,750, with a differential range of 60 to 65 per cent neutrophils, 30 to 35 per cent lymphocytes and 2 to 3 per cent monocytes. Daily sedimentation rates varied between 14 and 18 mm. per hour. Examination of the sputum showed occasional nonhemolytic streptococci. Extensive search failed to reveal yeasts, fungi or molds. Studies for the presence of acid-fast bacilli disclosed none. Repeated examinations of

gastric contents did not reveal tubercle bacilli. Ziehl-Neelsen staining of direct smears from the pleural fluid revealed Myco. tuberculosis. No myceliums were noted. The fluid was cultured on Sabouraud's maltose peptone agar and on Petragnini's medium. In four days small elevated waxy-like oval and round plaques measuring 3 to 10 mm. in diameter were observed on Sabouraud's medium. Within fourteen days these plaques were covered and surrounded by a snow white, fluffy and flakelike growth which penetrated deep into the medium (fig. 2). Smears from this culture revealed an intricate mycelial network with long branching septate hyphae with a formation of conidia and chlamydospores (fig. 3). Cultures were sent to the Registry of Fungous Diseases, Duke University School

Fig. 4.—Culture on Petragnini's medium. Note the fluffy white growth of C. immitis surrounding the confluent coarse gray-brown dirty growth of Myco. tuberculosis.

of Medicine, from which a confirmatory diagnosis of C. immitis was received. On the Petragnini medium a similar growth of C. immitis was noted on the seventh day, which reached maximum growth on the twenty-fifth day. On the fourth week numerous hard, wrinkled, elevated, coarse, brown-yellow colonies, measuring 14 to 18 mm. in diameter, were noted on this culture medium. Smears revealed characteristic tubercle bacilli. On the fifth week it was of great interest to note the Petragnini medium, on which was growing a coarse, homogeneous, confluent, dirty gray-brown growth of Myco. tuberculosis, surrounded by a fluffy, snowlike growth of C. immitis, the two apparently growing independently of each other (fig. 4).

Pleural fluid (5 cc.) was injected subcutaneously into the right groin of an adult male guinea pig. Seventeen days later the pig exhibited a swollen right testicle. The overlying skin was reddened and edematous. Microscopic examination of the testis revealed a suppurative orchitis. The draining lymph nodes were enlarged two to four times their usual size and were soft. On section, the entire nodal parenchyma was converted into a soft, yellow-gray necrosuppurating mass. Histologic examination revealed complete loss of nodal architecture. The lymphoid follicles could not be made out but were replaced by small granulomatous foci consisting of pyknotic lymphocytes, polymorphonuclear leukocytes and large mononuclear histiocytes. A number of these foci exhibited central necrotic cores consisting predominantly of karyorrhectic and karyolytic polymorphonuclear leukocytes. Within and occupying the central portions of the granulomas were double-contoured spheres measuring 10 to 50 microns in diameter (figs. 5 and 6). Within these spherules were numerous endospores. Budding was not observed. Interspersed throughout the cellular elements were large multinucleated giant cells
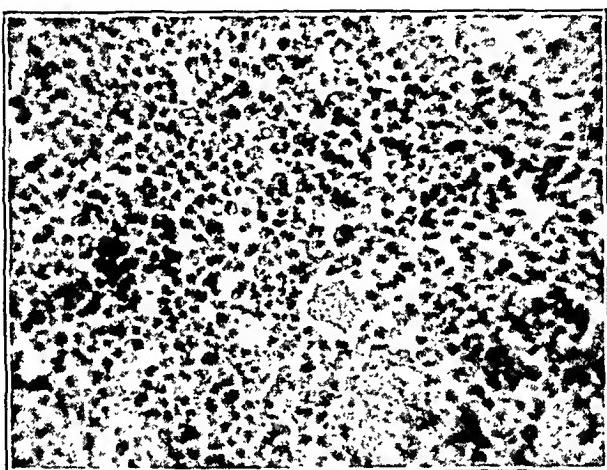
Fig. 5.—Focal granuloma from the inguinal lymph node of a male guinea pig. Note the double-contoured spherule of C. immitis. × 450.

of the Langhans type. The nuclei were deeply pyknotic and aggregated peripherally. The cytoplasm of these giant cells contained numerous spherules. However, a number of these granulomas revealed central eosin-staining caseation, surrounded by palisades of epithelioid cells containing clear reticular cytoplasm with deep vesicular nuclei. Scattered throughout were other Langhans' giant cells, the cytoplasm of which did not contain the characteristic spherules (fig. 7). Acid-fast stains revealed tubercle bacilli in these foci. Cultures of material from the lymph nodes on Sabouraud's and Petragnini's medium revealed beginning growth of C. immitis and Myco. tuberculosis within four and twenty-six days respectively. Serum was sent to the Stanford University School of Medicine, Department of Public Health and Preventive Medicine, for confirmatory serologic tests for coccidioidal infection. A complement fixation test gave a positive reaction (4 plus and 2 plus) in dilutions of 1:2 and 1:4 respectively but elicited a negative reaction in higher dilutions. A precipitin test with undiluted antigen gave a negative reaction. The conclusion reached from these serologic examinations were that the "findings indicate a coccidioidal infection which occurred a considerable time in the past and which does not seem to be progressive."
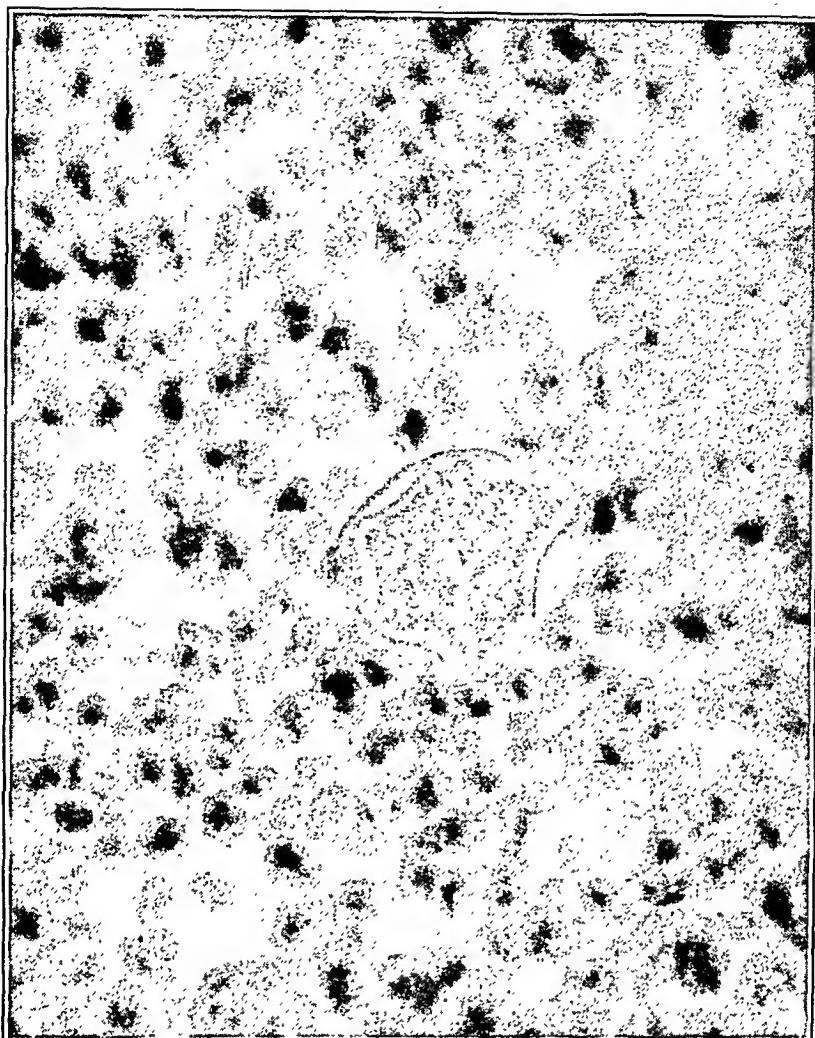
Fig. 6.—C. immitis. The immediate type cell surrounding the organism is a polymorphonuclear leukocyte.   × 980.

Fig. 7.—Multinucleated giant cell in a tuberculous focus.   Note the concentric palisading of epithelioid cells.   C. immitis is not present here.   Ziehl-Neelsen stains reveal tubercle bacilli in this area.   × 450.

COMMENT

This case affords interesting speculation with especial regard to pathogenesis. The combination of a slowly resolving pleural effusion on the right side accompanied with a complete collapse of the underlying lung together with a stationary nodule in the opposite lung suggests that the lesion at the left side was the older. The persistence of firm, well circumscribed lesions following an attack of coccidioidomycosis is well known. In this hospital 2 other patients had been observed with solitary parenchymal lesions persisting twelve to twenty-two months respectively following the acute infection. The patients remained asymptomatic for many months. From the roentgenologic standpoint both pathologic processes could be due to either tuberculosis or coccidioidomycosis. Colburn,[4] in a recent report of a series of seventy-five acute infections with coccidioidomycosis in soldiers, reported only 2 cases, or 2.7 per cent, in which there was massive pleural effusion. The effusion resolved slowly, and even after ninety days considerable pleural thickening remained. Neither of the 2 patients had a parenchymal lesion. An additional 10 per cent of these patients had mild and unusually localized pleural reactions. Colburn's division of his large group of patients into those primarily with patchy pneumonitis, with hilar adenitis and adenopathy, with pleural effusion, with cavitation or with a combination of these processes reflects the generally accepted classification arising not from coccidioidomycosis but from tuberculosis. From the roentgenologic changes alone, the two diseases in the majority of cases are similar.

Smith[3] made note of the fact that he had never seen a simple coccidioidal pleural effusion fail to absorb. Several persons, however, had been seen by him with a coccidioidal empyema, in 1 of whom it persisted for over one year. It has been impossible to obtain a complete history of our patient's first episode. It appears highly probable that this was a severe infection, since he was hospitalized for a period of six months. It is apparent that the onset of the spontaneous pneumothorax occurred while he was overseas. The exact nature of this incident remains obscure. It is possible that a subpleural tuberculous cavity had ruptured into the pleura, with a resultant bronchopleural fistula, and that during this process extension into a well localized and latent coccidioidal infection had occurred. It may well be, as Smith suggested, that a subpleural, coccidioidal cystlike cavity had ruptured and precipitated the trouble. The possibility of a cavity, in which both organisms had resided, which ruptured into the pleural cavity is remote but might be considered. There is nothing to indicate that there is a disseminated coc-

4. Colburn, J. R.: Roentgenological Types of Pulmonary Lesions in Primary Coccidioidomycosis, Am. J. Roentgenol. **51**:1-8 (Jan.) 1944.

cidioidal infection. The low sedimentation rate, the normal temperature and pulse, the absence of abnormal physical findings except in the chest, the progressive recovery of the patient, the absence of toxicity, the low titer of the complement fixation test and the negative precipitin reaction with undiluted antigen all point to the fact that this is not a progressive spreading infection but one which is essentially mechanical in nature.

SUMMARY

A case of a young soldier with coexisting active tuberculosis and coccidioidomycosis is presented. C. immitis and Myco. tuberculosis were both isolated from the pleural fluid by cultural methods and inoculation of a guinea pig.

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SEPTIC STAPHYLOCOCCEMIA SUCCESSFULLY TREATED BY PENICILLIN AND BACTERIOPHAGE

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SEPTIC staphylococcemia, its complications and sequelae have been a major problem for study by our group for many years. Several papers have appeared from time to time dealing with the use of bacteriophages in many hundreds. of patients and presenting in detail the therapeutic program in some of the more serious clinical varieties of this infection, such as osteomyelitis, septic thrombosis of the cavernous sinus, staphylococcic meningitis and staphylococcic endocarditis. The introduction of the sulfonamide drugs and subsequently of penicillin was followed by their enthusiastic use against staphylococcic infections, with success in many instances. More recently, streptomycin is being employed against the staphylococcus because of the well known but inadequately discussed failures in sulfonamide and penicillin therapy of infections with resistant staphylococci. At this time we wish to present the record of a patient with fulminant septic staphylococcemia, apparently complicated by localization on the endocardium and in the lumbar portion of the spine, in whom the infecting staphylococcus was remarkably resistant to penicillin and moderately resistant to bacteriophages in the culture tube. The patient was successfully treated by the use of these therapeutic agents in combination.

REPORT OF A CASE

S. D., a white woman aged 64, was admitted to the hospital on Dec. 31, 1944, with chills and fever which had begun on the previous day. The temperature on admission was 104.6 F., and clinical opinion favored a diagnosis of pneumonia, but roentgenologic examination revealed no evidence of gross pulmonary infiltration. There was an area of inflammation on the great toe of the left foot, about a large fissured corn, and this may have been the portal of entry for the infection.

The earlier part of her record at the hospital is shown in abridged form in the charts. Culture of the patient's blood taken on admission developed 13 colonies of Staphylococcus aureus per cubic centimeter of blood, and the succeeding cul-

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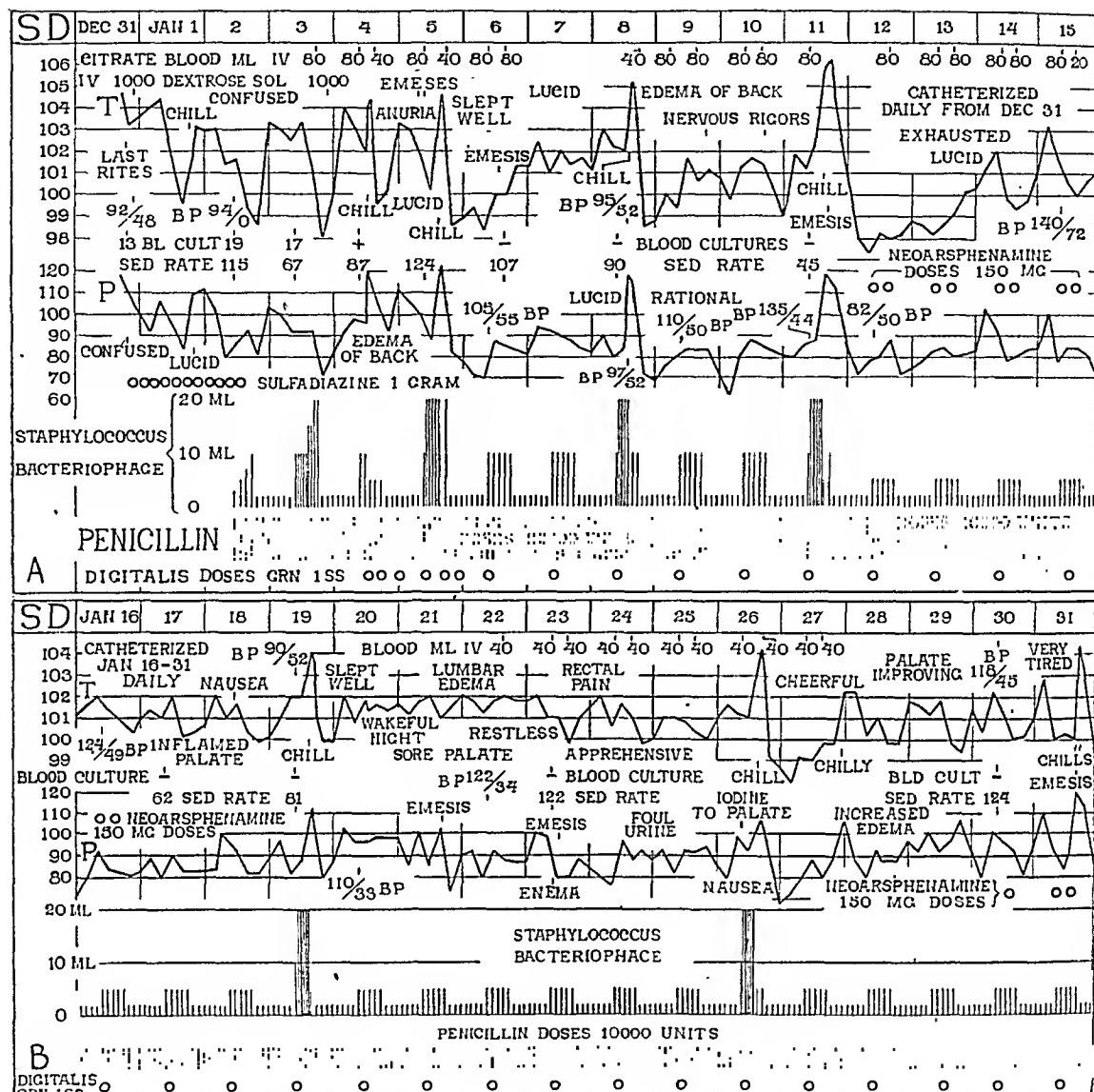
Chart 1.—A, abbreviated clinical record of S. D. from her admission, on Dec. 31, 1944, to Jan. 16, 1945. The extremely grave prognosis on admission was indicated by the high temperature, rapid pulse, low blood pressure and mental confusion. The first culture of the blood, taken on the evening of December 31, brought to development 13 colonies per cubic centimeter of the patient's blood, first recognized on the morning of January 2, at which time anti-infectious therapy for the staphylococcemia was initiated and the use of sulfadiazine discontinued. The culture of the blood taken on January 2 yielded 19 colonies per cubic centimeter of the patient's blood, that of January 3 yielded 17 and that of January 4 showed growth of less than 1 colony per cubic centimeter of blood. The subsequent cultures of the blood remained sterile. Blood was given by fractional transfusion, beginning with 80 cc. on the afternoon of January 3. It was necessary to catheterize daily. There was extensive edema over the lower region of the back after January 4. Penicillin dosage was 20,000 units every two hours given intravenously during the day and by intramuscular injection at night, from January 2 to January 12, and subsequently it was 10,000 units every two hours. Staphylococcus bacteriophage was given intravenously on January 2 in increasing doses of 3, 5, 7

and 10 cc., followed by the uniform doses of 2 cc. every two hours during the night. On January 3 another series of doses at intervals of approximately sixty minutes was given, 10, 10, 10, 10, 10, 15, 15, 20 and 20 cc., beginning at 9:30 a. m. and ending at 5:30 p. m., without recognized febrile reaction. However, the bacterial population of the blood stream was diminished in the next culture of the blood. On January 4 the two intravenous injections of 10 cc. of bacteriophage were followed by a definite chill shortly after midday. The behavior of the patient suggested a Hugh Young reaction, and the subsequent psychic improvement was in accord with this interpretation. On January 5 the doses of bacteriophage were pushed to higher levels, not precisely depicted on the chart: at 7:30 a. m., 2 cc.; 9:31 a. m., 10 cc.; 10:24 a. m., 20 cc.; 11:29 a. m., 30 cc. (heavy line); 12:30 p. m., 37 cc. (heavy line); 1:33 p. m., 50 cc. (heavy line); 2:31 p. m., 70 cc. (heavy line), and 5:29 p. m., 20 cc. On this day there was a typical Hugh Young reaction, beginning with chill at 3:15 p. m. and a rise in temperature to 104.6 F., with a subsequent rapid fall of temperature to 98.6 F. at 8 p. m. After two days of rest a shock reaction was again induced, on January 8, by another series of large doses of bacteriophage: at 7:30 a. m., 2 cc.; at 9:34 a. m., 10 cc.; at 10:35 a. m., 20 cc.; at 11:31 a. m., 30 cc. (heavy line); at 12:28 p. m., 40 cc. (heavy line); at 1:30 p. m., 30 cc. (heavy line); at 1:45 p. m., 20 cc. and at 3:37 p. m., 10 cc. Again there was a Hugh Young reaction, chill at 2 p. m., rise in temperature to 105.2 F. at 3:30 p. m. and diaphoresis and rapid decline of temperature to 98.6 F. at 8 p. m. Again on January 11 a series of increasing doses of bacteriophage was given: at 7:30 a. m., 2 cc.; 9:33 a. m., 10 cc.; 10:29 a. m., 20 cc.; 11:42 a. m., 30 cc. (heavy line); 12:50 p. m., 40 cc. (heavy line); 1:35 p. m., 50 cc. (heavy line); 2:39 p. m., 70 cc. (heavy line); 3:32 p. m., 5 cc. and 5:31 p. m., 10 cc. The Hugh Young reaction on this day was more severe, with chill, emesis, a rise in temperature to 106.2 F. and subsequent rapid decline to 97.4 F. at 8:00 a. m. on January 12. Neoarsphenamine in intravenous doses of 150 mg. was given twice daily on January 12, 13, 14, 15 and 16. The condition of the patient was still regarded as critical in the middle of January. The blood pressure reading of 140 systolic and 72 diastolic on January 15 was more satisfactory than the previously recorded figures. *B*, abbreviated clinical record of S. D. from Jan. 16 to 31, 1943. The cultures of the blood of January 17, 19, 23 and 30 remained sterile. The sedimentation rate remained abnormally high on all examinations. Use of a catheter had to be continued. There was also considerable difficulty with bowel elimination, and the colonic irrigation coupled with digital removal of impacted material on January 23 was followed by complaints of serious discomfort. Extensive inflammation of the roof of the mouth was an additional distressing complication, which finally responded to the application of tincture of iodine. On January 19 another intensive series of doses of bacteriophage was administered: at 7:30 a. m., 2 cc.; 9:31 a. m., 10 cc.; 10:30 a. m., 20 cc.; 11:32 a. m., 30 cc. (heavy line); 12:30 p. m., 50 cc. (heavy line); 1:30 p. m., 70 cc. (heavy line); 2:40 p. m., 50 cc. (heavy line); 3:30 p. m., 5 cc., and 5:30 p. m., 5 cc., followed by the usual intramuscular injection of 2 cc. beginning at 7:30 p. m. The Hugh Young reaction on this day was only moderately severe. On January 26 the intensive doses of bacteriophage were as follows: 7:30 a. m., 2 cc.; 9:32 a. m., 10 cc.; 10:34 a. m., 20 cc.; 11:30 a. m., 30 cc. (heavy line); 12:30 p. m., 50 cc. (heavy line); 1:32 p. m., 70 cc. (heavy line); 2:30 p. m., 100 cc. (heavy line); 3:29 p. m., 5 cc., and 5:31 p. m., 5 cc. On this day the temperature rose to 104.2 F. and it descended to 98.0 F. the next morning. Neoarsphenamine was again injected from January 30 to February 4. Administration of digitalis had been started on January 4, and maintenance doses were continued throughout the subsequent period covered by the charts. Toward the end of January the patient seemed to be losing ground, and on January 31 she had two distinct chills and a rise in temperature to 104.4 F., not clearly related to any therapeutic procedure.

tures, taken on January 2, 3 and 4, developed the same microbe. Study of this staphylococcus disclosed that it was resistant to penicillin, so that even 500 units of penicillin per hundred cubic centimeters of broth failed to cause the slightest recognizable inhibition of growth in the test tube. It was also rather resistant to the available bacteriophages, so that even after many serial filtrations complete clearing of the culture was not observed and the maximum lytic effect was read as 2 plus at four hours and zero at twenty-four hours. Subsequent serial filtrations failed to maintain this effect. Nevertheless the treatment was undertaken, although without expectation of success. On January 2 the patient was still mentally confused, with occasional lucid intervals. Moderate apical and aortic systolic murmurs were heard, both of which were thought to be of recent origin. Penicillin, 20,000 units by intravenous injection during the day and by intramuscular injection at night, was given from 11:33 a. m. on January 2 to January 12, and it was given thereafter in doses of 10,000 units at the same intervals. Stock staphylococcus bacteriophage was regularly injected along with the peni-
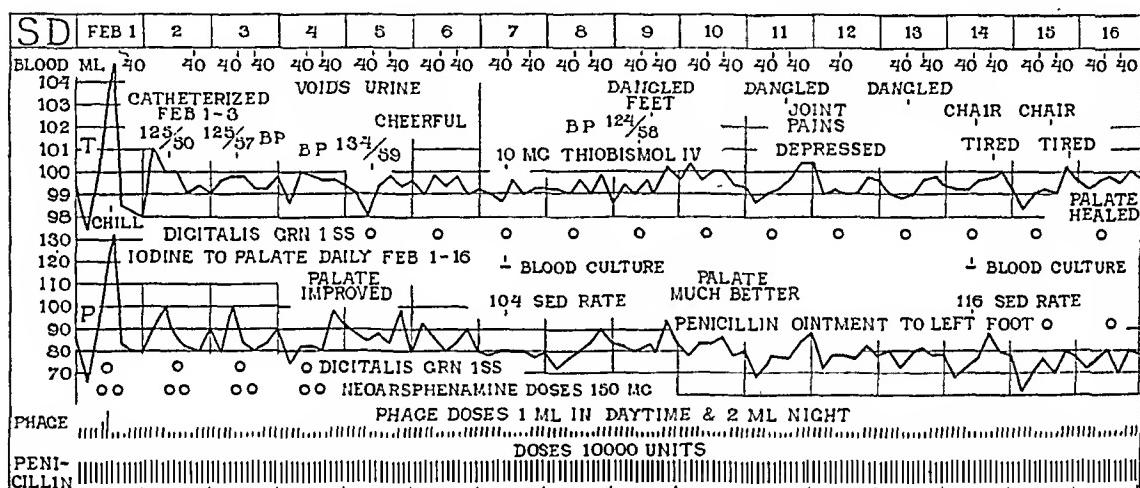
Chart 2.—Abbreviated clinical record of S. D. from Feb. 1 to 16, 1945. After the usual medication during the night of January 31, the dose of bacteriophage was decreased to only 3 cc. at 9:31 a. m. on February 1, followed by administration of 5 cc. at 11:35 a. m., along with the usual 10,000 units of penicillin at each injection. There was a chill beginning at 12:30 noon. Smaller doses of the bacteriophage were given thereafter. The small transfusions and the maintenance doses of digitalis were continued as indicated on the chart. Use of neoarsphenamine was discontinued after February 4. Urine was voided naturally after February 3. A single injection of thio-bismol was given on February 7 but not repeated. The intravenous administration of neoarsphenamine and thio-bismol served to supplement other anti-infectious therapy.

cillin but in varied doses, and on some days the bacteriophage was given every hour. The chart is not adequate in showing the details of dosage of bacteriophage but does give a general idea of it. The first dose of bacteriophage was 3 cc. injected intravenously along with the penicillin at 11:33 a. m. on January 2. This was followed at intervals of two hours by injections of 5, 7 and 10 cc. at 1:30, 3:32 and 5:30 p. m. respectively. Then, at 7:30 p. m. and on through the night, the dose of bacteriophage was 2 cc. given by intramuscular injection up to 7:30 a. m. inclusive. On January 3 the bacteriophage was given every hour in a dose of 10 cc. from 9:30 a. m. to 1:30 p. m. inclusive, making a total

of 50 cc. in the five doses. Then a dose of 15·cc. was given at 2:34 p. m. and repeated at 3:34 p. m., followed by 20 cc. at 4:43 and again 20 cc. at 5:32 p. m. In the eight hours from 9:30 a. m. to 5:32 p. m. she therefore received 120 cc. of bacteriophage intravenously. There was no .evident reaction. Her mental condition cleared somewhat at about 3 p. m., and there was profuse diaphoresis and lowering of temperature in the evening. At this time an increasing subcutaneous edema was observed, especially over the lumbar region and the buttocks but also on the arms.

On January 4 the dose of bacteriophage at 9:31 a. m. was 10 cc., and this dose was repeated at 11:26 a. m. The patient went into a chill at 12:15 p. m., which lasted thirty minutes, and her temperature rose to 104.4 F. The dose of bacteriophage at 1:20 p. m. was reduced to 5 cc., and this was repeated at 3:31 p. m. and at 5:31 p. m., after which the usual injections of 2 cc. were given through the night. At 2:15 p. m. on this day 1,200 cc. of urine was taken by catheter, and, although some urine was voided naturally at times, catheterization was required daily during the period from December 31 to January 15. On January 5, after a delirious night, she was mentally · clear. She vomited at 7:15 a. m. and again at 9:15 a. m. Bacteriophage was injected intravenously in increasing doses to produce a shock: 10 cc. at 9:29 a. m.; 20 cc. at 10:24 a. m.; 30 cc. at 11:29 a. m. (indicated· by heavier line on chart 1 *a*) ; 37 cc. at 12:30 p. m.; 50 cc. at 1:33 p. m., and 70 cc. at 2:31 p. m., making a total of 217 cc. in about five hours. The chill started at 3:15 p. m. and terminated at 3:55 p. m., with an elevation of temperature to 104.6 F. at 4 p. m., followed by diaphoresis at 4:20 p. m. and sharp decline of temperature to 98.6 F. at 8 p. m. This appeared to be·a fairly typical Hugh Young reaction and was regarded as encouraging. At 5:30 p. m., after an interval of three hours because of the chill, an injection of 20 cc. of bacteriophage was given along with the usual dose of penicillin and followed by administration of 40 cc. of citrated blood through the same needle. Subsequently the doses of bacteriophage were 2 cc. each during the night and 10 cc. each during the day, at intervals of two hours, until the morning of January 8. On this day, after blood had been taken for determination of the sedimentation rate and culture, an injection of 10 cc. of bacteriophage was given along with the penicillin at 9:34 a. m., followed by 20 cc. at 10:35 a. m.; 30 cc. at 11:31 a. m.; 40 cc. at 12:28 p. m.; 30 cc. at 1:30 p. m., and 20 cc. at 1:45 p. m. The dose of 50 cc. scheduled for 1:30 p. m. was partly withheld at that time because the patient said that she felt chilly, but when a genuine chill did not appear, the 20 cc. to complete the prescribed dose was administered at 1:45 p. m. At about 1:55 p. m. there was a definite chill, which lasted until 2:25 p. m., and at 3:10 p. m. the temperature reached 105.2 F. and then it descended to 98.6 F. at 8 p. m. The patient remained asleep, and there was profuse diaphoresis. The edema of the back persisted, but otherwise the patient seemed to be improved. The regular doses of bacteriophage, of 2 cc. during the night and 10 cc. during the day, were continued during January 9 and 10. On January 11 the doses of bacteriophage were stepped up to 10 cc. at 9:33 a. m.; 20 cc.·at 10:29 a. m.; 30 cc. at 11:42 a. m. (represented by a heavier line in the chart) ; 40 cc. at 12:50 p. m.; 50 cc. at 1:35 p. m., and 70 cc. at 2:39 p. m.. The chill began at 2:45 p. m. and lasted fifty minutes. During the chill the patient was given an intravenous injection of 20,000 units of penicillin and 5 cc. of bacteriophage at 3:32 p. m. There was some mental confusion, and the temperature rose to 105.8 F. at 3:45 p. m. At 4:30 p. m. she vomited a large amount of undigested food and was incontinent. At 5:30 p. m. the temperature was 106.2 F., but nevertheless she was given an intra-

venous injection of 20,000 units of penicillin and 10 cc. of bacteriophage at this time. The patient remained semiconscious until about 10:30 p. m., at which time she began to sweat profusely and became mentally alert. This severe Hugh Young reaction exhausted her strength, but in other respects her condition seemed to be improved. The doses of bacteriophage were reduced to 5 cc. during the day and were continued at 2 cc. during the night, along with doses of penicillin reduced to 10,000 units every two hours. Neoarsphenamine, in doses of 150 mg., was given twice daily from January 12 to 16.

Chart 1 B shows the abridged record from January 16 to 31. Catheterization was still required during this period. An extensive inflammation of the palatal mucous membrane was a new and troublesome complication, which finally disappeared after frequent applications of tincture of iodine. Edema over the lumbar region persisted. Fractional transfusions, usually 40 cc. twice daily, were given from time to time. Cultures of the blood remained sterile, but the continued fever and the high sedimentation rate indicated persistent activity of the staphylococcic infection, probably on the valvular endocardium and possibly in other localizations not-readily detected. On January 19 the doses of bacteriophage were again stepped up to induce a shock reaction: 10 cc. was given at 9:31 a. m.; 20 cc. at 10:30 a. m.; 30 cc. at 11:32 a. m.; 50 cc. at 12:30 p. m.; 70 cc. at 1:30 p. m., and 50 cc. at 2:40 p. m., making a total of 230 cc. of bacteriophage in approximately five hours. As the injection was being given at 2:40 p. m. the patient began to tremble and remarked that she was about to have a chill, and because of this the injection was limited to 50 cc. at this time. Actually she did go into a genuine chill, lasting thirty minutes, and her temperature rose to 104.0 F. at 4 p. m. Nevertheless she was given a small dose of 5 cc. of bacteriophage at 3:30 p. m. along with the penicillin. The Hugh Young reaction on this day was rather mild, and the patient was comfortable later in the evening. On January 23 there was a somewhat distressing fecal impaction, with consequent rectal trauma, which caused some apprehension. On January 26 another bacteriophage shock was induced. The doses of bacteriophage given intravenously were as follows: 10 cc. at 9:32 a. m.; 20 cc. at 10:34 a. m.; 30 cc. at 11:30 a. m.; 50 cc. at 12:30 p. m.; 70 cc. at 1:33 p. m., and 100 cc. at 2:30 p. m., making a total of 280 cc. of bacteriophage in five hours. The chill became distinctly evident at 3:15 p. m. and continued forty minutes, to 3:55 p. m. During this period of chilling, an intravenous injection of 5 cc. of bacteriophage and 10,000 units of penicillin was given at 3:29 p. m. The temperature rose to 104.2 F. at 4:30 p. m., and it descended promptly to 99.2 F. at 8 p. m. A restful night followed. The edema over the lumbar region and the buttocks increased, and the region was tender to pressure. The usual doses of bacteriophage and penicillin were given from January 27 to 31 inclusive. At 9:29 a. m. on January 30 the blood pressure reading was 118 systolic and 45 diastolic. On this day the patient was emotionally upset by war news concerning a son in the air service. Administration of neoarsphenamine in doses of 150 mg. twice daily was started again on the afternoon of January 30. From 3 to 5 a. m. on January 31 she complained of severe pain in the right thigh and leg, and in the morning she felt extremely tired after the restless night. However, she was cheerful during the day until 4:20 p. m., when she vomited and went into a chill, which lasted forty-five minutes, with a rise of temperature to 104.4 F. at 5:45 p. m. At 6:55 p. m. she had another chill, lasting ten minutes. These chills seemed to be without relation to any medication, and they may have been due to emboli. Nevertheless, because we had previously observed an increased sensitiveness to bacteriophage when

staphylococcemia was progressing favorably, it was decided to reduce the dose somewhat. Hence at 9:31 a. m. on February 1 the dose of bacteriophage was 3 cc., and at 11:35 it was again 5 cc. Curiously enough, the patient had chills again from 12:30 to 1 p. m., and her temperature rose to 104.8 F. at 1:30 p. m. It seemed that this reaction was induced by the smaller amounts of bacteriophage injected intravenously, namely 3 cc. at 9:31 a. m. and 5 cc. at 11:35 a. m. Therefore the subsequent doses of bacteriophage were at a lower level, 1 cc. intravenously every two hours in the daytime and 2 cc. by intramuscular injection every two hours at night. The doses of citrated blood, of digitalis, of neoarsphenamine and of penicillin are clearly indicated on the charts. There was decided improvement in the record after February 2, and the use of a catheter was discontinued on February 3. The inflammation of the mouth subsided, and it was entirely healed on February 16. The patient dangled her feet on February 9 and tried sitting in a chair on February 14.

The subsequent record at the hospital extends to June 16, 1945, and it seems unnecessary to present it in detail. From February 17 to February 22 the temperature did not exceed 100.0 F. at any observation. The injections of bacteriophage and penicillin were continued as before. The large corn on the plantar surface of the great toe of the left foot, which was thought to be the portal of infection, was treated by application of penicillin ointment daily, beginning on February 13. On February 20 this massive corn had separated, so that it was lifted off in one piece without any bleeding, leaving a smooth epidermal surface. On February 23 the patient was out of bed, sitting in a chair in the morning and again for a half hour in the afternoon. When sitting, she suffered pain in the lumbar region and at times also in the thighs and legs. At 6:15 p. m. there was a definite chill, which lasted thirty-five minutes, with a rise in temperature to 101.8 F. at 6:50 p. m. Culture of blood taken during the chill remained sterile. The temperature did not exceed 100.0 F. again until March 6. On February 26 the use of penicillin was discontinued and the dosage of bacteriophage reduced to 2 cc. twice daily. The patient was out of bed in a chair one or more times a day, and she walked a short distance. However, the effort seemed to cause more pain in the back and in the lower extremities, and early in March she became discouraged about trying to leave her bed. Because of the continued complaints of pain in the lumbar region and in the lower extremities, a roentgenologic study of the lumbar area of the spine was made on March 6, and this disclosed articular erosion and necrosis of the neighboring articular surface between the third and fourth lumbar vertebrae, along with advanced osteoarthritic changes in the thoracic region as well as the upper part of the lumbar region of the spine. It was not possible to decide whether or not there had been a recent complicating staphylococcic infection superimposed on the old structural alterations. On account of these findings it was decided to avoid excessive pressure and strain on the lumbar portion of the spine until a suitable supporting corset could be prepared. She was allowed to be about in a wheel chair in a reclining position with adequate support to avoid strain or pressure on the back. Use of digitalis, which had been taken since January 4, was discontinued on March 6.

The visit to the department of radiology on March 6 was followed by a period of slight fever, with maximum temperatures of 100.4 F. on the evening of March 6, 101.6 F. on March 7, 100.8 F. on March 8, 100.4 F. on March 11 and 100.8 F. on March 12. Subsequently there was no temperature observed higher than 100.2 F. from March 13 to April 7 inclusive. The intravenous injections of 2 cc. of bacteriophage twice a day were continued during this period. She was

up in a wheel chair daily and walked with assistance on some days. However, on April 8 the temperature rose to 101.0 F. at 6 p. m. She had been on the sun roof in a wheel chair from 1:15 to 3:15 that afternoon and remained out of bed until 5:45 p. m. Shortly thereafter she complained of severe pains in the right arm and right leg, and her pulse became irregular. Physical examination did not aid in understanding this episode, which may, nevertheless, have been related to overexertion. Again the temperature rose to 101.2 F. at midnight on April 12 and to 101.4 F. at 4 a. m. on April 13. An abdominal binder was applied shortly after midnight, and this seemed to relieve the intense lumbar discomfort.

There was another febrile period, beginning on April 17, with a temperature of 101.0 F. at midnight, followed by high points of 101.6 F. on April 18; 101.4 F. on April 19; 101.0 F. on April 20, and 100.4 F. on April 21, again associated with irregular pulse. At this time she was emotionally disturbed because of serious illness of a relative, concerning whom she had only fragmentary information. However, this would not seem to be a wholly satisfactory explanation of the elevated temperature.

On April 23 there was a disturbance of another kind. After a restful night and a comfortable day, during which she received her usual intravenous doses of 2 cc. of bacteriophage at 9:33 a. m. and at 3:33 p. m., the patient had a definite chill at 4:55 p. m., lasting until 5:30 p. m. At this time there was severe pain in the legs, arms and back of the neck. The temperature rose rather slowly, registering 101.6 F. at 4:55 p. m.; 102.2 F. at 5:30 p. m.; 103.0 F. at 6:35 p. m., and 104.0 F. at 8 p. m., and it descended to 101.6 F. at 10 p. m.; 100.3 F. at 10:30 p. m., and 98.6 F. at 4 a m. on April 24. The patient slept well. On April 24 and 25 she appeared well as usual. Then on April 26 there was a repetition of the upset. The patient sat in a chair from 3:15 to 4:15 p. m. and received her afternoon injection of 2 cc. of bacteriophage at 3:32 p. m., followed by 40 cc. of citrated blood. At 4:15 p. m. she drank a little wine (40 cc.) The chill started at 4:55 p. m. and lasted until 5:30 p. m. The temperature rose to 102.0 F. at 5:30 p. m. and 103.0 F. at 7 p. m. and then descended to 101.8 F. at 8 p. m. and 99.8 F. at 11:40 p. m. Subsequently the patient slept well. April 27 was uneventful, although the patient received intravenous injections of 2 cc. of bacteriophage and 40 cc. of citrated blood at 9:29 a. m. and 3:34 p. m., as usual. On April 28, however, there was a chill from 12:40 to 1:30 p. m., with a rise of temperature to 102.0 F., and again at 5:20 to 6 p. m., with the temperature rising to 103.4 F. at 7 p. m. The patient slept well after 10 p. m. These disturbances may have been due to (1) increased sensitiveness to the bacteriophage, (2) pyrogenic agents in the bacteriophage used, (3) pyrogenic substances in the citrated blood, (4) changes in the course of the patient's infection or (5) other, unrecognized, factors. We are inclined to ascribe them to some fault in the bacteriophage used or to increased sensitivity of the patient.

From April 29 to May 11 the temperature rose above 100.0 F. only once, when it was recorded as 100.4 F., at 8 p. m. on May 6. During this time the dose of bacteriophage was 1 cc. twice daily. The patient was out of bed much of the time and seemed to be definitely convalescent. On May 12 there was severe pain in the arms and legs throughout the day, and the temperature rose to 101.6 F. at 8 p. m. On each of the following days from May 13 to May 22 inclusive, the highest temperatures observed were 101.4, 102.0, 101.8, 100.2, 100.6, 100.0, 99.8, 100.4, 100.0 and 100.4 F. respectively. During this period of ten days the patient was out of bed in a chair and walking short distances as she desired. She complained continually of pain in the lower limbs, and there was definite edema over the left lumbar region.

Apparently the lumbar region of the spine had not yet healed so as to afford adequate support without undue pressure on nerve structures, and there were some difficulties in adjusting the special supporting corset. On May 14 activity out of bed was restricted to thirty minutes daily, and on May 16 the dose of bacteriophage was further reduced to 0.5 cc. twice daily, and the use of the bacteriophage was discontinued altogether on May 18. After May 22 the recorded temperature did not again exceed 100.0 F. Restrictions on activity were gradually relaxed, so that by June 1 she was out of bed most of the day. On June 13 she was out of the hospital on pass from 1 : 45 to 5 p. m., and on June 16 she was discharged.

Cultures of the blood of this patient were made at intervals of a week or oftener from December 31 to June 13. The specimens of December 31 and January 2, 3 and 4 yielded the staphylococcus. All others were sterile. The sedimentation rate of the blood was also tested once a week, and it was always abnormally high. During the last two months in the hospital, the weekly examinations from April 11 to June 13 inclusive gave the following figures: 60, 100, 115, 87, 35, 78, no examination, 82, no examination and 55. These readings represent millimeters of sedimentation at sixty minutes (Westergren technic), for which the normal figure should not exceed 18 mm. There was therefore some apprehension in regard to a possible persistent low grade activity of infection in the lumbar vertebrae.

Since her discharge the patient has continued to improve. In June 1946 she reported steadily satisfactory progress, with almost complete recovery of her usual health. The supporting corset is still used, and the back is still weak, so that she usually carries a cane when walking out of doors. The feet have remained free from the bothersome callosities which formerly caused so much discomfort.

<center>COMMENT</center>

There has been presented an objective and somewhat detailed account of the care in the hospital from Dec. 31, 1944 to June 16, 1945 of a woman aged 64 years who had a long-standing disorder of the lower part of the vertebral column and associated callosities and deformity of the feet, complicated by an acute septic staphylococcemia, beginning on December 30, and apparently giving rise to staphylococcic endocarditis and staphylococcic osteoarthritis of the lumbar region of the spine. The staphylococcus isolated in cultures of the blood was remarkably resistant to penicillin in the culture tube and also fairly resistant to the available bacteriophages. After the therapeutic use of these two agents in combination the bacteria promptly disappeared from the blood stream, and after a prolonged period of continued treatment the internal metastatic localizations of the infection were brought to a state of arrest, an outcome which was wholly unexpected in the earlier days of this illness.

The remarkable synergistic action of bacteriophages in combination with penicillin has been observed by Himmelweit [1] in Fleming's laboratory at St. Mary's Hospital, London, England. The therapeutic value

1. Himmelweit, F.: Combined Action of Bacteriophage and Penicillin on Staphylococci, Lancet 2:104-105 (July 28) 1945.

of such combined or conjoined action has been indicated in previous reports [2] from our own laboratory. S. D., in the case reported, presents an outstanding example of an infection in which the staphylococcus was resistant to penicillin and to bacteriophage as individual agents, and yet the conjoined therapy was followed by recovery.

There are many obscure details in the behavior of a patient with staphylococcemia. The use of penicillin alone does not ordinarily induce the chill and the rise and decline in temperature which characterize the Hugh Young [3] reaction. Possibly the penicillin acts to restrain or to inhibit growth of the bacteria without operating to increase phagocytosis or bacteriolysis to an appreciable degree. Other agents, such as the merbromin of Young and especially the bacteriophages, appear to alter the bacteria so that they are more rapidly taken up by phagocytic cells [4] and more rapidly disintegrated by bacteriolytic action, resulting in the Hugh Young reaction, which resembles the paroxysm of early tertian malaria. Undoubtedly there are other chills which occur in the course of septic disease which are even less well understood.

Giving citrated blood by the method of fractional transfusion [5] has been our method of choice in the treatment of septic conditions for many years. It is most acceptable to the patients and not too great a burden to the physician when intravenous medication with other agents is regularly given.

SUMMARY

1. A woman aged 64 years, with moderate chronic disability due to changes in the lower part of the thoracic and lumbar regions of the spine, spinal cord and lumbar nerves, complicated by acute septic staphylococcemia, apparent septic endocarditis and metastatic osteoarthritis of the lumbar vertebrae, has been successfully treated by injections of penicillin and staphylococcus bacteriophage.

2. The staphylococcus in this case was resistant to penicillin alone and moderately resistant to bacteriophage alone.

3. The patient was well and active in June 1946, some seventeen months after the last culture of the blood was positive for pyrogens and about twelve months after her discharge from the hospital.

2. MacNeal, W. J.; Poindexter, C. A., and Marty, F. N.: Apparent Arrest of Staphylococcal Endocarditis, Am. Heart J. **29**:403-408 (March) 1945. MacNeal, W. J.; Filak, L., and Blevins, A.: Conjoined Action of Penicillin and Bacteriophages, J. Lab. & Clin. Med. **32**:974-981 (Sept.) 1946.

3. MacNeal, W. J.: Specific Therapeutic Shock—The Hugh Young Reaction, Arch. Surg. **43**:579-582 (Oct.) 1941.

4. MacNeal, W. J.; Frisbee, F. C., and Slavkin, A. E.: Mechanism of Bacteriophage Action in Staphylococcus Bacteremia, Proc. Soc. Exper. Biol. & Med. **30**:12-14 (Oct.) 1932.

5. MacNeal, W. J., and Straub Neil, M. E.: Fractional Transfusion, J. Lab. & Clin. Med. **22**:842-845 (May) 1937.

HEMOLYTIC STREPTOCOCCIC SORE THROAT

The Poststreptococcic State

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IT HAS been known for more than thirty years that recovery from hemolytic streptococcic infection of the respiratory tract is frequently complicated by the development during convalescence of a variety of disorders including fever, arthritis, carditis and nephritis.[1] These conditions are clearly not the result of a direct invasion of the remote tissues by streptococci present in the throat during the initial illness and may be regarded as "late nonsuppurative complications"[2] of hemolytic streptococcic disease. The importance of this concept has been emphasized by the increasing body of evidence which indicates that rheumatic fever is one of the late complications of infection by hemolytic streptococci.

Recent investigation has greatly increased the information available in regard to the bacteriology, immunology and natural history of streptococcic infection and its complications. In a series of papers[3] the

1. Escherich, T., and Schick, B.: Scharlach, Vienna, A. Holder, 1912.

2. Keefer, C. S.: The Late Nonsuppurative Disorders of Hemolytic Streptococcal Diseases, Texas State J. Med. **35**:457, 1939.

3. (a) Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcal and Nonstreptococcal Respiratory Disease: A Comparative Clinical Study, Arch. Int. Med. **78**:369 (Oct.) 1946. (b) Rantz, L. A.; Spink, W. W., and Bois-

pertinent literature has been reviewed, and the clinical manifestations of the intial phase of acute sore throat caused by group A hemolytic streptococci as observed in military personnel have been described, as well as the suppurative and nonsuppurative complications that followed. The latter disorders were specifically considered in two papers [3d,e] in which it was stated that the development of rheumatic fever was invariably preceded by a hemolytic streptococcic infection of the respiratory tract. A nonarthritic poststreptococcic continuing disease, with or without electrocardiographic evidence of carditis, was also observed. The pathogenesis of these disorders was considered, and the possible importance of reinfection by new types of group A hemolytic streptococci was emphasized.

The suggestion was made that all the arthritic and nonarthritic nonsuppurative poststreptococcic syndromes be considered together and be regarded as manifestations of the "poststreptococcic state." It is the purpose of this paper to describe the continuing disease that followed sore throat caused by group A hemolytic streptococci and to characterize the "poststreptococcic state" in detail.

METHODS

All patients suffering from disease of the respiratory tract of any type were admitted to certain wards in the station hospital, where they were seen by one of us. A history was obtained, a physical examination performed and cultures of materials from the throat and nose made. Patients discovered, on clinical and bacteriologic grounds, to be suffering from infection by hemolytic streptococci were transferred to special wards, where a permanent trained nursing staff was maintained, which permitted the execution of therapeutic and other investigative programs. These patients were studied by means of a variety of laboratory procedures. Cultures were made repeatedly of materials from the nose and throat, and the isolated hemolytic streptococci were classified serologically by the precipitin technics of Lancefield.[4] Serial white blood cell counts, erythrocyte sedimentation rates (Westergren) and electrocardiograms were obtained. Each patient was studied for not less than three weeks and frequently for a longer period.

vert, P. J.: Hemolytic Streptococcus Sore Throat: The Course of the Acute Disease, ibid. **79**:272 (March) 1947. (*c*) Spink, W. W.; Rantz, L. A.; Boisvert, P. J., and Coggeshall, H.: Sulfadiazine and Penicillin for Hemolytic Streptococcus Infections of the Upper Respiratory Tract: An Evaluation in Tonsillitis, Nasopharyngitis, and Scarlet Fever, ibid. **77**:260 (March) 1946. (*d*) Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, ibid. **76**:131 (Sept.) 1945. (*e*) Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Abnormalities in the Electrocardiogram Following Hemolytic Streptococcus Sore Throat, ibid. **77**:66 (Jan.) 1946. (*f*) Rantz, L. A.; Rantz, H. H.; Spink, W. W., and Boisvert, P. J.: Streptococcic and Nonstreptococcic Diseases of the Respiratory Tract: Epidemiological Observations, ibid. **77**:121 (Feb.) 1946.

4. Lancefield, R. C.: Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci, in Harvey Lectures, 1940-1941, Baltimore, Williams & Wilkins Company, 1941, vol. 36, p. 251.

THE CLINICAL MATERIAL

The nature of the group studied has been described elsewhere.[5] In brief, examples of sore throat caused by group A hemolytic streptococci, with and without rash, occurring in military personnel were intensively studied. Sixty-nine cases of this disease were selected in the previous analysis [3d] as possible examples of poststreptococcic nonsuppurative continuing disease. The criteria used for the differentiation of these cases were the presence of arthritis, electrocardiographic evidence of carditis or an erythrocyte sedimentation rate greater than 20 mm. per hour three weeks after the onset of the acute respiratory disease. Prolonged disability on the basis of definite local suppuration in the form of peritonsillar abscess, otitis media or paranasal sinusitis was observed in 15 additional men, who were excluded from consideration.

All the information obtained from the study of these examples of hemolytic streptococcic sore throat has been recorded on charts and exhaustively reanalyzed. As a result, certain cases which were disregarded have been included with the examples of nonsuppurative disease. Fifteen cases in which the erythrocyte sedimentation rate was persistently elevated were transferred to the group of suppurative complications, since sinusitis was probably present.[3b]

Complete detailed observations were available in 299 cases. Serial electrocardiograms were obtained in 185. The erythrocyte sedimentation rate at the end of three weeks was greater than 20 mm. per hour in 85. Local suppuration was definitely or probably responsible for the prolonged reaction of the tissue in 30 of these cases.

Seventy-two cases remained [5a] as possible examples of poststreptococcic nonsuppurative continuing disease on the basis of persistent unexplained abnormalities of the erythrocyte sedimentation rate or because of other clinical manifestations of illness.

CLINICAL OBSERVATIONS

Arthritis.—The course in 19 cases of hemolytic streptococcic sore throat was complicated by the development of arthritis. Fifteen of the patients, who were hospitalized as having typical examples of acute rheumatic fever, have been previously described.[3d] The cases of 4 additional patients, in whom the symptoms in the joints were less severe and who received ambulatory treatment, are included in this report. The essential clinical and laboratory data are presented in table 1. . Cases 6 and 10 were described and illustrated elsewhere.[3d]

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5. Rantz, Boisvert and Spink.[3a,d] Rantz, Rantz, Spink and Boisvert.[3f]

5a. Infection by group A hemolytic streptococci was positively established in all these cases by the presence of rash or a significant antistreptolysin or antifibrinolysin response.

TABLE 1.—*Poststreptococcic Arthritis: Clinical and Laboratory Data*

Case No.	Infecting Type	Day of Onset of Arthritis	Duration of Arthritis, Days	Late Fever			Erythrocyte Sedimentation Rate*					Electrocardiogram				Severity of Arthritis	Comment
				Day of Onset	Duration, Days	Maximum Temperature, F.	First	Second	Third	Most Rapid Rate	Day First Normal	Day First Done	Day First Abnormal	Duration of Abnormality, Days	Key No.†		
1	Untypable	3	18	3	18	102.0	Not done	41/10	110/20	110/20	70‡	8	14	10	23	Severe	
2	46	17	7	16	9	104.0	20/2	10/9	100/20	111/24	48	19	19	12	25	Moderate	
3	36	15	5	13	11	103.0	35/2	22/12	97/19	97/19	44	8	Normal	Normal	..	Severe	
4	30,30 and 19	63	10	63	5	102.0	48/2	92/26	38/36	106/70	90	36	36	50	26	Severe	Clinical reinfection
5	6 and 19	16	11	19	6	101.0	59/4	19/12	90/20	102/23	48	20	Normal	Normal	..	Severe	Inapparent reinfection
6	19	14	10	22	25	102.0	55/2	30/9	28/22	104/29	67	9	9	150	30	Severe	Pericarditis, days 25 to 65; Complete heart block
7	30	10	4	12	8	103.0	8/2	30/7	57/13	90/19	40	7	7	35	28	Minimal	Clinical reinfection;
8	19 and 3	39	11	39	9	102.0	Not done	Not done	46/35	103/51	90	44	44	8	29	Severe	relapse of rheumatic fever on day 110
9	Untypable	35	10	35	3	99.0	Not done	Not done	37/18	93/38	50	36	36	45	31	Severe	
10	3, 46 and 30	38	10	36	8	105.0	14/2	6/18	9/30	75/41	71	9	Normal	Normal	..	Severe	Two clinical reinfections
11	3 and 1	42	8	40	2	100.0	12/3	4/9	3/22	27/41	49	9	Normal	Normal	..	Moderate	Inapparent reinfection
12	19	28	35	Afebrile	Afebrile	98.6	41/3	38/10	29/22	94/32	67	12	Normal	Normal	..	Moderate	
13	3	20	20	Afebrile	Afebrile	98.6	60/3	93/11	31/28	31/28	40	18	Normal	Normal	..	Minimal	Relapse of rheumatic fever on day 72
14	36	2	65	Afebrile	Afebrile	98.6	94/4	Not done	44/23	44/23	90	10	10	10	27	Mild	
15	26	20	14‡	Afebrile	Afebrile	98.6	29/3	31/9	37/22	37/22	44	9	Normal	Normal	..	Mild	Soles sore
16	30	12	9	Afebrile	Afebrile	98.6	70/2	Not done	42/23	42/23	39	38	38	7	21	Mild	Ankles, knees, elbows and shoulders painful
17	36	15	14	Afebrile	Afebrile	98.0	12/3	11/19	33/26	33/26	34	36	Normal	Normal	..	Mild	Knees and right elbow painful and swollen
18	36	19	14	Afebrile	Afebrile	98.0	42/2	9/8	43/19	43/19	34	34	Normal	Normal	..	Minimal	Pain in shoulder, elbow and wrist
19	36	25	14	22	17‡	99.4	32/3	27/8	30/22	39/39	39	Not done	Not done	Not done	..	Mild	Aching in knees and elbows

* Numerator is erythrocyte sedimentation rate, denominator is day following onset of streptococcic infection on which test was done.
† Refers to number of the case under which electrocardiograms were described in a previous paper.[3e]
‡ Last day of clinical observation.

The joints were first involved from three to sixty-three days after the onset of the acute streptococcic sore throat. A rise in temperature usually preceded this event by one to three days if fever was to be associated with the arthritic disease. Seven patients remained afebrile. The maximum temperature of the other patients varied from 99.0 to 105.0 F. but was less than 101.0 F. in only 2. Arthritis was regarded as severe in 8, moderately severe in 3, mild in 5 and minimal in 2 cases. An elevated temperature persisted during the arthritic illness for two to twenty-five days and was usually terminated by the administration of salicylates.

The erythrocyte sedimentation rate was abnormally rapid in every case during the arthritic phase of the disease. The maximum rates varied from 27 to 110 mm. per hour and were usually attained a few days after the involvement of the joints had become manifest. If the duration of abnormality of the erythrocyte sedimentation rate is determined in relationship to the initial streptococcic infection, it is discovered that the first normal rate was recorded after thirty days in no patients, after sixty days in 12 and after ninety days in the remainder. Recovery, as estimated by this test, occurred in 5 cases within forty days.

Electrocardiographic evidence of carditis was obtained in 9 of these cases. The nature and duration of the abnormalities observed have been previously described,[3e] and certain of these data are recapitulated in the table. The development of valvular cardiac disease was not recognized in any of these men during the period of study. Transient apical systolic murmurs were heard in several. Gallop rhythm in 1 and heart block in another patient were definite clinical signs of myocarditis. Persistent pericarditis was observed in a third patient.

In a previous paper [3d] it was noted that a true "latent" or quiescent period, separating the initiating streptococcic infection from the arthritic complication, was only occasionally observed in these cases. Abnormal electrocardiograms were present days to weeks before the onset of arthritis. The erythrocyte sedimentation rate remained abnormally rapid or increased during this intermediate period in 9 and came or remained within normal limits in 6 cases. Two were inadequately studied, and arthritis developed in 2 within three days of the onset of the initial streptococcic infection. Malaise was present during the "latent period" in several cases in which abnormal erythrocyte sedimentation rates were demonstrated during this interval.

No serologic type of hemolytic streptococcus was more likely than any other to incite the development of arthritis, since types 19, 30 and 36. which appear most frequently as the cause of the initiating infection in these cases. were also among the common types isolated in all cases of streptococcic disease in the station in which the study was made.[3f]

'It may be of importance to record the fact that arthritis never followed monotype infections by the common type 17 (18 cases) or a food-borne epidemic strain of type 1 (over 250 cases).[6]

The importance of reinfection by new serologic types of hemolytic streptococci in the pathogenesis of the arthritic poststreptococcic state has been previously suggested.[3d] To recapitulate, bacteriologic or bacteriologic and clinical evidence of such reinfection was obtained in 5 of these cases, 3 of which were those in which a definite latent period occurred. It should also be noted that 75 men who were in various stages of convalescence from hemolytic streptococcic sore throat were exposed to reinfection by a type 1 Streptococcus during a food-borne
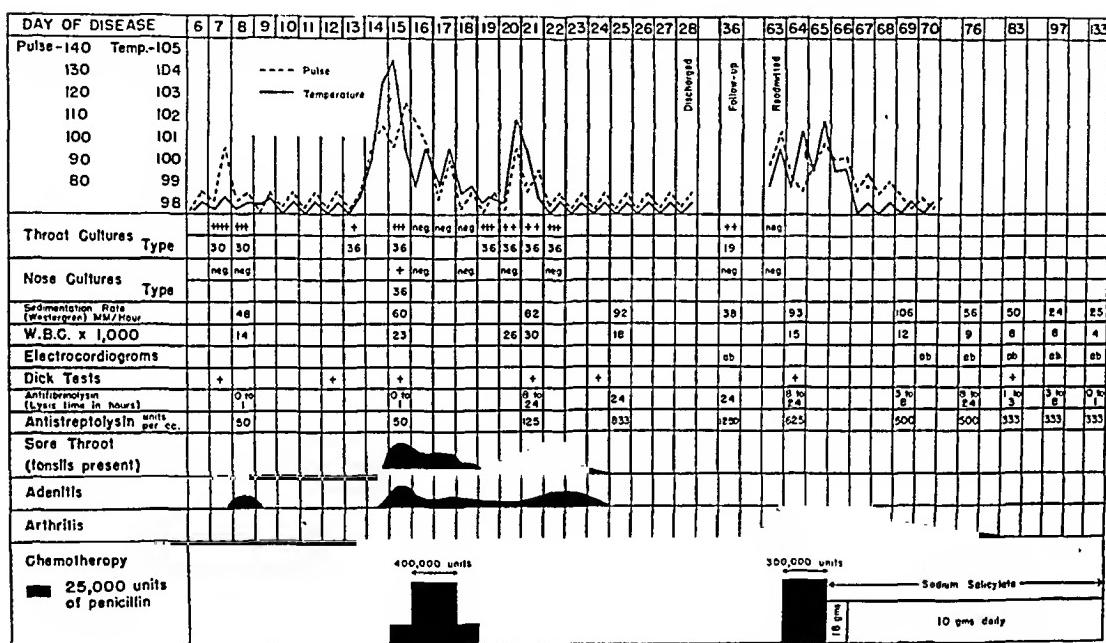
Chart 1.—L. J. H., aged 36, had poststreptococcic arthritis and fever (rheumatic fever) following a series of reinfections by different serologic types of hemolytic streptococci. There was no previous rheumatic fever.

epidemic, and a number showed definite laboratory and/or clinical evidence of invasion of the tissue by this organism. Arthritis developed in 3 of these men. This is approximately the same frequency of occurrence of involvement of the joints as that observed for the whole group.

Clinical summaries and charts of the course in 2 cases are appended, since each presents features of great interest.

CASE 4 (chart 1).—A 36 year old man was admitted to the hospital on the sixth day of a mild respiratory illness. The erythrocyte sedimentation rate and

· 6. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Hemolytic Streptococcus Sore Throat: Simultaneous Infection of a Large Number of Men by a Single Type, Arch. Int. Med. **76**:278 (Nov.-Dec.) 1945.

leukocyte count were elevated, and large numbers of type 30 hemolytic streptococci were recovered from the pharynx. Eight days later he suffered a reinfection by streptococci of type 36. This illness was inadequately treated with penicillin, and clinical and bacteriologic relapse occurred. He was clinically well by the twenty-seventh day and was discharged from the hospital, although the erythrocyte sedimentation rate and leukocyte counts remained abnormally elevated. When he returned for a follow-up examination on the thirty-sixth day, he was well but the erythrocyte sedimentation rate was 38 mm. per hour and the electrocardiogram abnormal (case 26[3e]). Type 19 streptococci were present in the throat at this time. Twenty-seven days later he returned to the hospital febrile and with severe arthritis of the knees and elbows. The erythrocyte sedimentation

OF DISEASE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	40
CULTURES																																		
TYPE	30	30											30		30																			
ROCARDIOGRAMS							AB										AB	AB						AB	AB		AB							AB
TATION RATE (GREN) MM/HR		8					30						57					90					50								46	19
CULTURES	NEG																																	
X 1,000		13					10						16					12					8								6	5
RINOLYSIN TIME IN HOURS)		O TO I					O TO I						O TO I					I TO 3					O TO I								I TO 3	I TO 3
EPTOLYSIN PER CC)		100					100						100					50					50								100	100
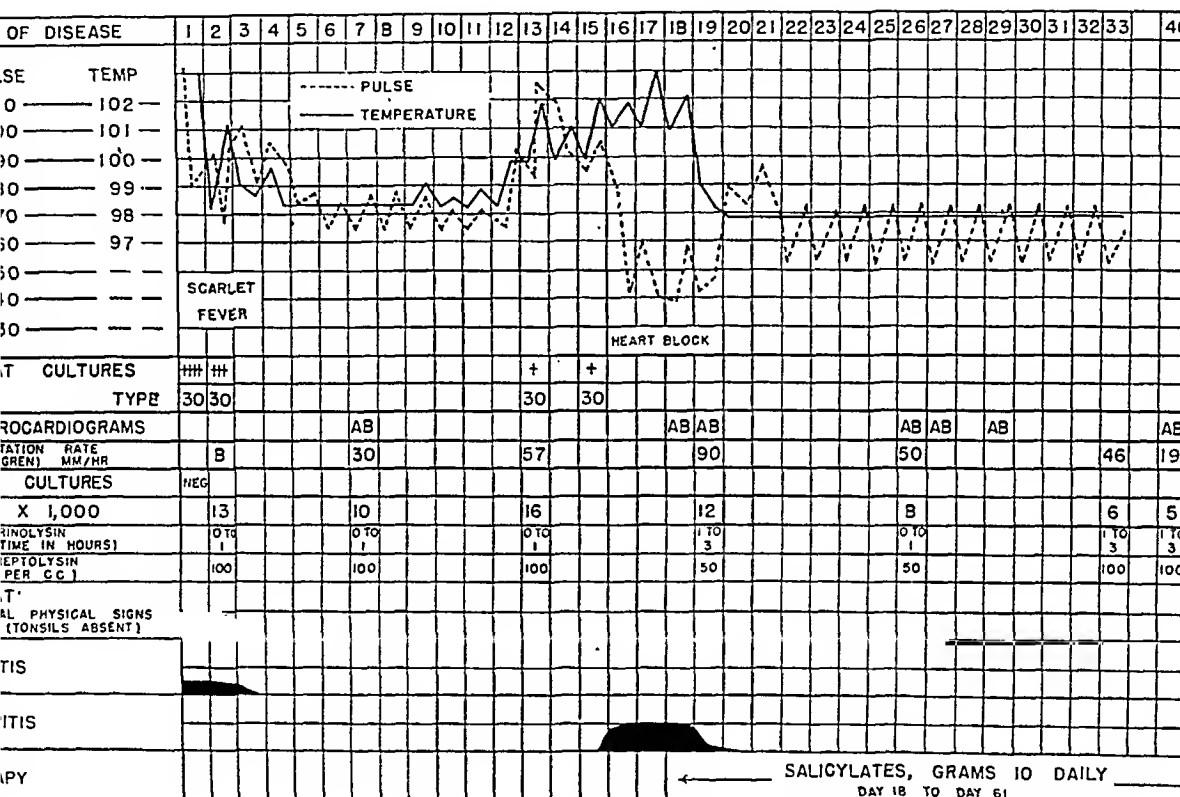
Chart 2.—Poststreptococcic arthritis, fever and complete heart block were seen in G. M. McC., aged 19.

rate had become more rapid, but the electrocardiogram presented abnormalities similar to those observed earlier.

The course of the disease was that of a severe attack of rheumatic fever, and he was not completely recovered on the one hundred and thirty-third day of the disease.

Comment.—This case illustrates the course of events in a man who suffered a clinical and also an inapparent reinfection by hemolytic streptococci of types different from those causing the initial illness. A true latent period was not established, and an abnormal erythrocyte sedimentation rate and electrocardiogram were discovered sixteen days after the last acute sore throat and twenty days before the appearance of arthritis.

CASE 7 (chart 2).—A 19 year old youth was admitted to the hospital on the first day of a moderately severe infection by type 30 hemolytic streptococci.

A cutaneous rash was present. He made an uneventful recovery, but the erythrocyte sedimentation rate, which had been normal on admission, became progressively more rapid over the next twelve days. An electrocardiogram (case 28 [3a]) on the seventh day was abnormal, the T waves being flat in lead I and inverted in leads II and III. High temperature appeared on the twelfth day. Four days later, the pulse rate fell sharply, and complete heart block was demonstrated by electrocardiography. Minimal arthritis of the shoulders and hips was also noted at this time. The erythrocyte sedimentation rate was then 90 mm. per hour. After institution of salicylate therapy, the course was that of moderately severe rheumatic fever, and he had recovered by the forty-sixth day. Neither an antistreptolysin nor an antifibrinolysin response occurred.

Comment.—An initial streptococcic infection with rash (scarlet fever) was followed by a progressive increase in the reaction of the tissue as measured by the erythrocyte sedimentation rate. The electrocardiogram was abnormal on the seventh day. Five days later, poststreptococcic fever developed, followed in four days by the appearance of minimal arthritis and complete heart block. A true "latent period" was entirely absent.

Summary.—Hemolytic streptococcic sore throat was followed in 19 cases by the appearance of arthritis of varying degrees of severity. Fever was often associated with this complication. The erythrocyte sedimentation rate was invariably elevated during the arthritic phase of the illness and remained so for more than thirty days in every case. Abnormal electrocardiograms, indicating the presence of carditis, were discovered in 9 cases, in 3 of which there was also clinical evidence of myocardial involvement. Definite signs of permanent damage to the valves of the heart were not obtained during the period of study. Evidence of a continuing reaction of the tissue in the form of abnormal erythrocyte sedimentation rates and electrocardiograms was usually present during the "latent period," separating the acute suppurative illness from the arthritic phase of the disease.

LATE FEVER

The convalescence of 14 patients with hemolytic streptococcic sore throat was complicated by a recrudescence of fever. The essential data derived from a study of these men are presented in table 2. This event occurred after a period of normal temperature from five to nineteen days in length. Careful study failed to disclose a suppurative complication in any case as an explanation for the late elevation in temperature.

The maximum poststreptococcic temperature varied from 100 F. to 104 F. but was less than 101 F. in 6 of 11 cases in which detailed records of the temperature were available. An elevated temperature persisted for from two to more than forty days. Neither antibacterial nor salicylate chemotherapy was instituted in any case, since it was desirable to study the unaltered natural history of the illness.

The erythrocyte sedimentation rate was abnormally rapid during the period of late fever in 13 cases and remained so for more than twenty

Table: TABLE 2.—*Poststreptococcic Fever: Clinical and Laboratory Data*

Case No.	Infecting Type	Late Fever			Erythrocyte Sedimentation Rate *					Electrocardiogram				Comment
		Day of Onset	Duration	Maximum Temperature, F.	First	Second	Third	Rate During Fever	Day First Normal	Day First Done	Day First Abnormal	Duration of Abnormality, Days	Key No.†	
20	36	5	2	101.0	14/2	89/8	11/21	89/8	21	8	Normal	Normal	..	
21	19, 28 and untypable	9	9	100.0	30/2	25/8	20/21	29/14	30	8	8	Over 24	16	Illustrated in text
22	19 and 36	12	28	100.0	52/4	69/15	68/20	68/29	50	15	Normal	Normal	..	Illustrated in text
23	17	6	7	101.5	41/2	87/8	32/20	90/14	29	7	7	7	..	Illustrated in text
24	46	6	12	100.0	50/2	73/8	18/20	73/8	20	8	Normal	Normal	..	Illustrated in text
25‡	36	10	7	102.0	....	....	....	.....	..	Not done	Not done	..	9	Illustrated in text
26	30	15	5	100.0	17/2	3/8	48/21	48/21	Over 21	Not done	Not done	Not done	..	
27	26	10	4	101.0	12/3	10/9	10/22	7/14	Unknown	9	Normal	Normal	..	
28	10	13	8	99.8	40/3	25/8	35/24	27/19	Over 24	14	Normal	Normal	..	
29	19	10	Over 40	100.0	44/2	63/9	72/21	87/17	Over 68	12	Normal	Normal	..	Illustrated in text
30	19	Unknown	Unknown	99.6	17/3	44/8	25/33	25/33	Over 33	10	Normal	Normal	..	Fever discovered in outpatient follow-up
31	3	6	2	104.0	45/2	32/8	15/21	32/8	21	8	8	Over 14	12	Fever discovered in outpatient follow-up
32	30 and 1	Unknown	Unknown	100.0	33/2	1/13	37/21	44/33	Over 33	13	13	Over 20	10	Fever discovered in outpatient follow-up
33	30, untypable and 26	Unknown	Unknown	100.0	27/3	16/9	25/53	35/44	Over 44	9	25	Under 19	17	Fever discovered in outpatient follow-up

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which test was done.

† Refers to number of the case under which electrocardiograms were described in a previous paper.[3e]

‡ Data on this case is given in the text.

days in all, for more than thirty days in 5 and for more than forty days in 3 cases.

Serial electrocardiograms were obtained for 13 of these patients, and evidence of carditis was discovered in 5. The abnormalities were similar to those that were observed during arthritic poststreptococcic disease but were not so pronounced, nor were they as persistent. Clinical signs of carditis were not discovered, nor was permanent cardiac valvular disease diagnosed in any of these cases during the relatively brief period available for continued observation.

Malaise was severe in most of these men during the late febrile illness, and it frequently continued after the temperature had returned to normal.

Evidence of continuing reaction of the tissue in the form of an elevated erythrocyte sedimentation rate was demonstrable during the afebrile intermediate period in 2 of the 4 cases in which the late fever appeared fourteen days after the onset of the initial streptococcic disease. In the others, the interpretation of observations during the "latent period" was impossible because fever reappeared so quickly after the termination of the initial illness.

No single serologic type of hemolytic streptococcus predominated as the etiologic agent in the initial streptococcic infection preceding the development of late fever. Bacteriologic or bacteriologic and clinical evidence of reinfection by a new type was obtained in 4 cases.

Five of these examples of poststreptococcic fever will now be illustrated and described.

CASE 21 (chart 3).—A 19 year old youth was admitted to the hospital on the first day of a severe sore throat caused by type 19 hemolytic streptococci. The erythrocyte sedimentation rate was 30 mm. per hour and the leukocyte count 15,000 per cubic millimeter. He reacted positively to the Dick test, but no rash was observed. His reaction to the Dick test had become negative by the twenty-ninth day. He recovered uneventfully, but there was a recurrence of fever associated with a recrudescence of cervical adenitis on the ninth day, which persisted for twelve days. During this time he felt ill, and headache was severe. There was no clinical evidence of sinusitis, and roentgenograms of the chest were normal. The erythrocyte sedimentation rate remained moderately elevated, and the electrocardiograms (case 16 [3e]) obtained on the eighth day and later were abnormal. Type 28 streptococci had become the predominant flora of the nose and throat by the twenty-eighth day.

He was discharged from the hospital before complete recovery had occurred. Another febrile episode began on the twenty-ninth day, and he was readmitted to the hospital. Untypable streptococci were now present in large numbers, but there was no clinical evidence of a new suppurative lesion in the throat. A diffuse macular rash was noted over the trunk, but no Koplik spots appeared. The erythrocyte sedimentation rate was not decidedly elevated, but the electrocardiogram was still abnormal. The temperature returned to normal, and he was discharged. No further follow-up was possible.

Comment.—An example of late fever with carditis and cervical adenitis, appearing five days after the termination of the initial suppurative phase of acute hemolytic streptococcic sore throat is illustrated by this case. This episode may have been related to a reinfection by a new type of Streptococcus. Fever reappeared later, in association with a rash, and another type of Streptococcus was isolated from the throat. The exact nature of the latter process could not be ascertained.

CASE 22 (chart 4).—A 25 year old man was admitted to the hospital on the second day of a severe sore throat caused by type 36 hemolytic streptococci. He received 30 Gm. of sulfadiazine in six days and improved over a five day period, but withdrawal of the drug was followed by a clinical relapse, with recrudescence of the abnormal physical signs in the throat and neck and return of fever. The erythrocyte sedimentation rate and leukocyte count remained elevated for two weeks but were falling on the twenty-third day, at which time he felt well. Type 19 streptococci had become the predominant organisms four days later in the flora of the throat and nose. A notable increase in the erythrocyte sedimentation rate, which persisted until the fifteenth day, was closely associated with this event. The electrocardiogram was normal on three occasions.

Low grade fever was present from the twelfth to the forty-third days, when he was transferred to a convalescent barracks. He felt well until the twenty-ninth day, when easy fatigability followed by loss of weight was noted. Physical examinations and roentgenograms of the chest revealed nothing remarkable.

Full clinical recovery, with return of a sense of well-being, did not occur until the fifty-fifth day, at which time the erythrocyte sedimentation rate was still 19 mm. per hour. Fifty days later, he was well and the physical examination revealed no cardiac or other abnormalities.

Comment.—Sore throat caused by type 36 hemolytic streptococci was complicated by relapse following the withdrawal of administration of sulfadiazine and an inapparent reinfection by type 19 streptococci. The latter event was followed by a prolonged period of disability associated with low grade fever, malaise, loss of weight and a rapid erythrocyte sedimentation rate. Complete recovery did not occur until the fifty-fifth day of the illness.

CASE 23 (chart 5).—A 35 year old man was admitted to the hospital on the first day of a severe sore throat caused by type 17 hemolytic streptococci. He was afebrile by the fourth day, and he appeared to be recovering. A sharp rise in temperature associated with a decided increase in malaise occurred on the sixth day. No abnormalities were discovered on the physical examination to explain this event. A definite increase in the erythrocyte sedimentation rate and leukocyte count was discovered, and serial electrocardiograms revealed a transient inversion of the T wave in lead III. He was afebrile by the thirteenth day, but complete recovery, with return of the erythrocyte sedimentation rate to normal, did not occur until the fourth week of illness.

Comment.—The condition in case 23 is an example of poststreptococcic fever of seven days' duration, beginning on the sixth day and not explained by extension of the suppurative process. There was an increase in the erythrocyte sedimentation rate and leukocyte count and questionable transient electrocardiographic evidence of carditis.

CASE 25 (chart 6).—A 24 year old man was admitted to the hospital on the first day of a moderately severe sore throat caused by type 36 hemolytic streptococci, from which he recovered rapidly and uneventfully, the erythrocyte sedimen-
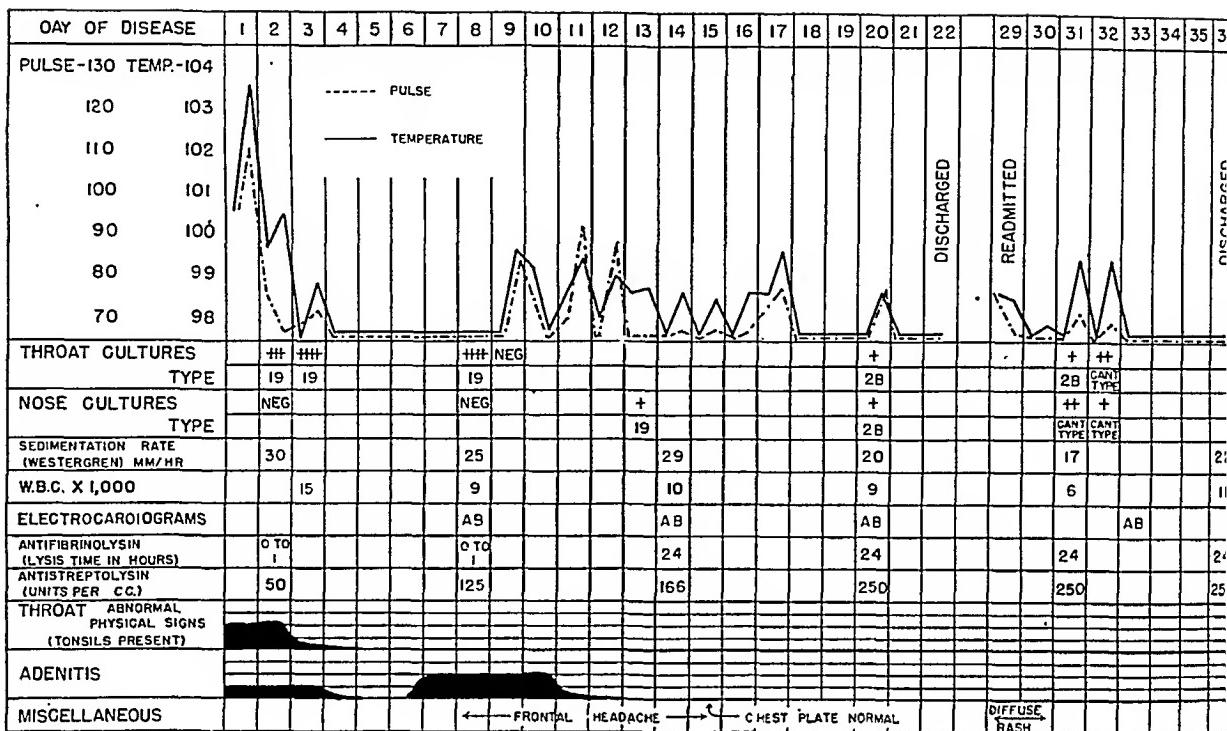
Chart 3.—Two episodes of poststreptococcic fever associated with carditis were observed in E. G. C., aged 19.
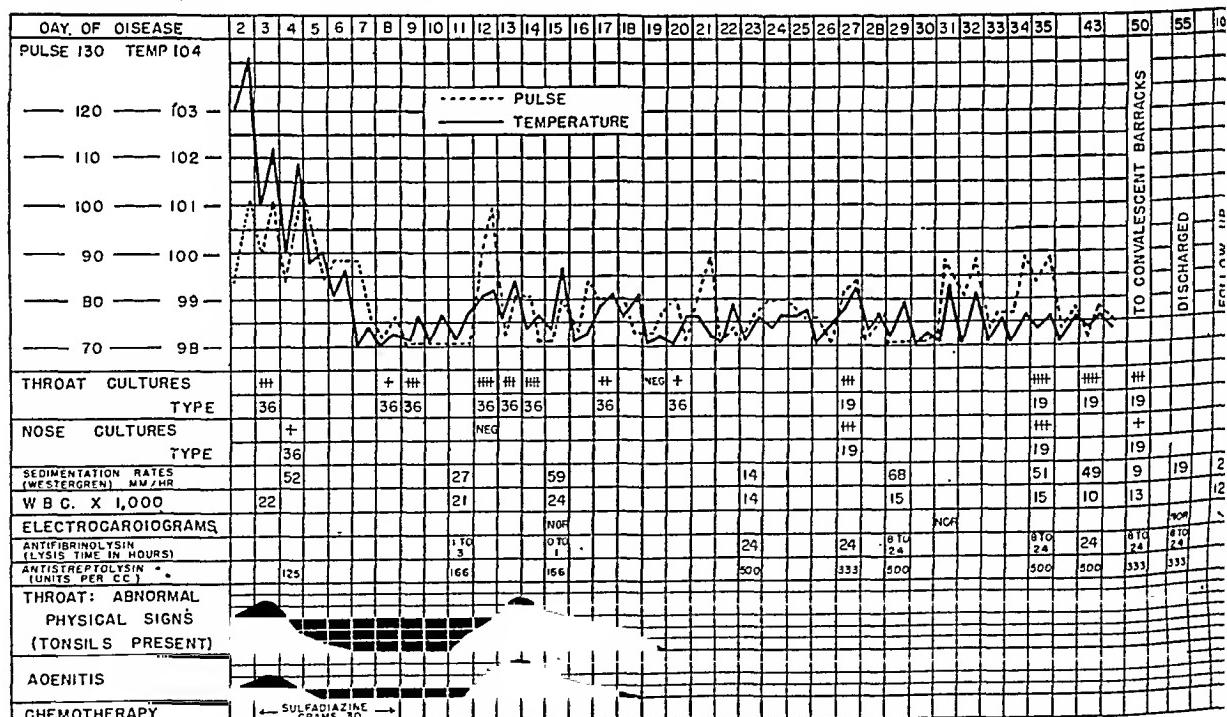
Chart 4.—Prolonged low grade poststreptococcic fever, malaise and persistently elevated erythrocyte sedimentation rate were evidenced by P. H., aged 25.

tation rate being 6 mm. per hour on the tenth day. Headache, anorexia and fever appeared on the eighteenth day, and he reentered the hospital. The erythrocyte sedimentation rate was abnormally rapid, and an electrocardiogram revealed the presence of a decidedly prolonged P-R interval (case 9 [3e]). His fever abated on the twenty-sixth day, and he was discharged although the erythrocyte sedimentation rate had increased. Three days later another febrile episode occurred, and he again was admitted to the hospital. The erythrocyte sedimentation rate was still abnormal, and the degree of heart block increased. He promptly became afebrile, but moderate tachycardia persisted. He was discharged, against advice, and returned to work. When seen in follow-up on the forty-third day he felt well, but

OF DISEASE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
·130 TEMP.-104 / 120 103 / 110 102 / 100 101 / 90 100 / 80 99 / 70 98																						DISCHARGED
T CULTURES	++	++				NEG								NEG						NEG		
TYPE	17	17																				
CULTURES	+++					NEG														NEG		
TYPE	17																					
ITATION RATE (RGREN) MM/HR		41						87						90						32		
X 1,000		15						19				11								11		
ROCARDIOGRAMS							AB							NOR						NOR		
INOLYSIN (IME IN HOURS)		0 TO 1						0 TO 1					24							3 TO 8		
EPTOLYSIN PER CC.)		50						100						250						250		
AT: ABNORMAL PHYSICAL SIGNS NSILS PRESENT)	−																					
TIS																						
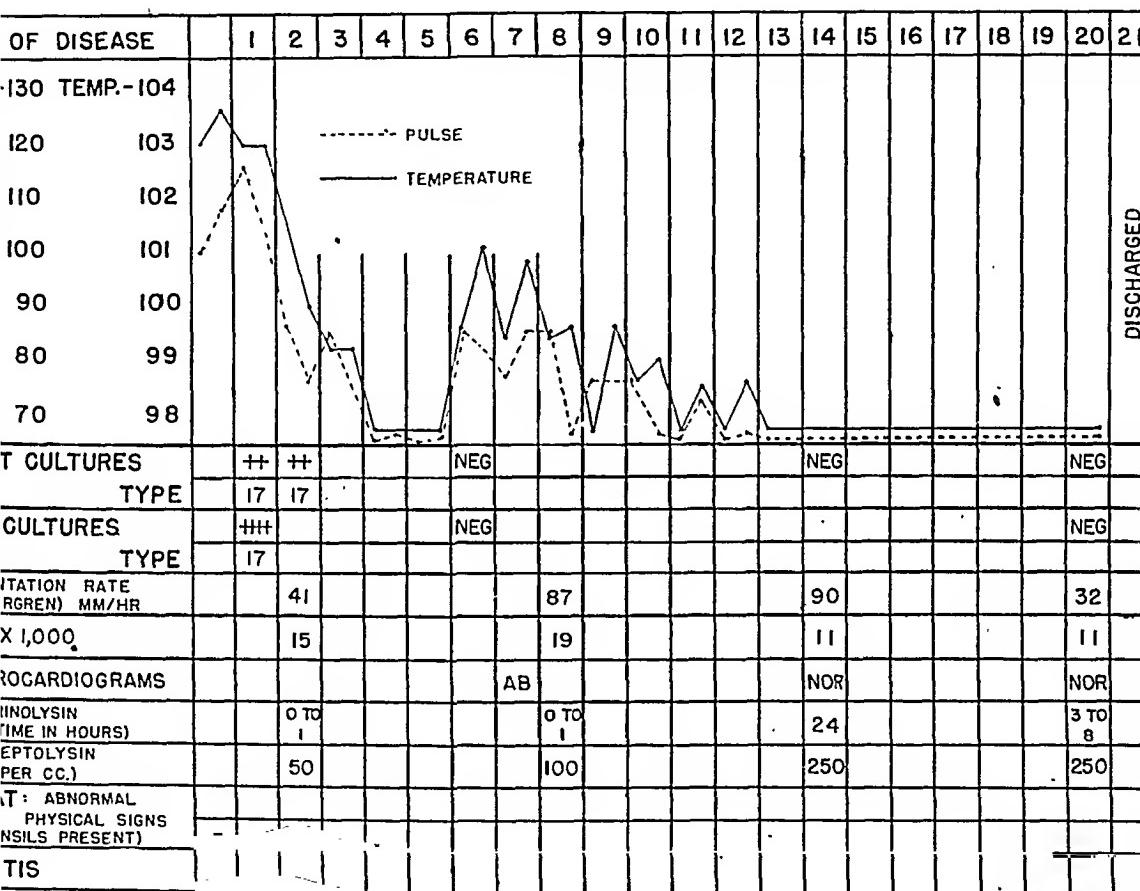
Chart 5.—Poststreptococcic fever, with minimal evidence of carditis, was observed in W. E. G., aged 35.

the erythrocyte sedimentation rate was 20 mm. per hour and the P-R interval prolonged.

Comment.—This is a case in which a monotype infection was followed by a true latent period. Later, two episodes of poststreptococcic fever associated with carditis supervened. Complete recovery had not occurred by the forty-third day.

CASE 29 (chart 7).—A 34 year old man was admitted to the hospital on the first day of a moderately severe sore throat caused by type 19 hemolytic strepto-cocci, from which he recovered uneventfully after the administration of 400,000 units of penicillin in thirty-two hours. He was approximately afebrile by the fourth day, and he remained so for five days. During this time the leukocyte count fell

to 10,000 per cubic millimeter. On the ninth day low grade fever appeared, and it continued until the patient's discharge. Simultaneously, the erythrocyte sedimentation rate was discovered to have become more rapid, and leukocytosis had recurred.

He was transferred to a convalescent barracks and was seen in follow-up on the seventeenth day, when he was febrile and the erythrocyte sedimentation rate was extremely rapid. He had become afebrile by the twenty-first day, and by the twenty-sixth day the erythrocyte sedimentation rate had become slower but was

DAY OF DISEASE	1	2	3	4	5	6	7	8	9	10	11	19	20	21	22	23	24	25	26	27	28	31	32	33	34	35	36	43
PULSE / TEMPERATURE (graph)											DISCHARGED	READMITTED									DISCHARGED	READMITTED					DISCHARGED	FOLLOW-UP
THROAT CULTURES	+++	+++						+++	+++			+	NEG									NEG						
TYPE	36	36						36	36			36																
NOSE CULTURES								+++	+++			NEG	NEG															
TYPE								36	36																			
SEDIMENTATION RATE (WESTERGREN) MM/HR			21						6			29									57			22				20
W.B.C. X 1,000			13						16			12									9			9				12
ELECTROCARDIOGRAMS																AB						AB						AB
ANTIFIBRINOLYSIN (LYSIS TIME IN HOURS)			8 TO 24						3 TO 8			8 TO 24								24			1 TO 3				0 TO 1
ANTISTREPTOLYSIN (UNITS PER CC)			125						125			166								166			166				166
THROAT — ABNORMAL PHYSICAL SIGNS (TONSILS PRESENT)																												
ADENITIS																												
MISCELLANEOUS												FRONTAL HEADACHE AND COUGH										FRONTAL HEADACHE AND FEVER						

Chart 6.—Two episodes of poststreptococcic fever associated with carditis were observed in W. P., aged 24.

still abnormal. From the ninth to the twenty-sixth day he felt ill, ate poorly and lost 12 pounds (5.4 Kg.) in weight.

Because he had not regained his full strength and was fatigued easily on moderate activity, he was readmitted to the hospital on the fifty-fourth day for further study. During the following fifteen days he was essentially afebrile and felt fairly well, but the erythrocyte sedimentation rate became progressively more rapid, being 41 mm. per hour on the sixty-eighth day. Leukocyte counts and roentgenograms of the chest were normal. Serial electrocardiograms throughout the illness were normal.

His condition on discharge on the sixty-ninth day was unsatisfactory in that his strength was below normal and he felt ill. Further follow-up was not possible.

Comment.—Here is an example of a case in which a period of disability of more than two months was initiated by a monotype hemolytic streptococcic infection of the respiratory tract. During this entire period, easy fatigability and malaise were associated with a rapid erythrocyte sedimentation rate and, at times, low grade fever. There was no evidence of carditis.

Summary.—The convalescence of certain patients with hemolytic streptococcic sore throat was complicated by a recrudescence of fever.
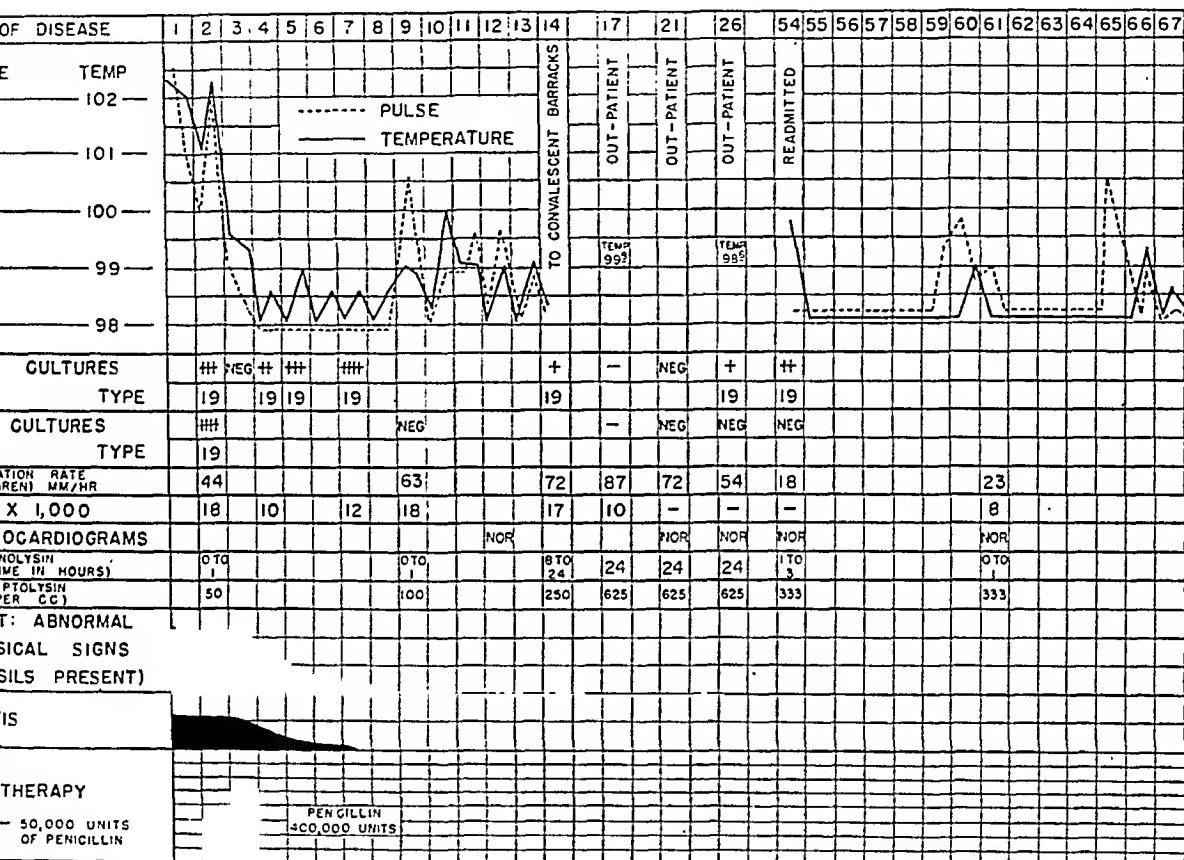
Chart 7.—J. G. O., aged 34, had prolonged poststreptococcic fever, malaise and a persistently elevated erythrocyte sedimentation rate.

The late febrile illness was associated with an elevated erythrocyte sedimentation rate, which frequently persisted for several weeks. Electrocardiographic but not clinical evidence of carditis was obtained in more than one third of this group.

These cases closely resemble those described previously in which rheumatic fever followed infection by hemolytic streptococci, except for the absence of arthritis. Important differences, however, were present. The late fever without involvement of the joints appeared earlier, was less severe, as estimated by the height of temperature and degree of abnormality of the electrocardiogram and erythrocyte sedimentation rate,

and was of shorter duration than in those cases in which arthritis was present. It should be emphasized that there was overlapping between the two groups in regard to the severity and duration of all these abnormalities.

CARDITIS

Electrocardiographic evidence of carditis was obtained for 11 patients convalescent from hemolytic streptococcic sore throat in whom arthritis and late fever were absent. The cases have been described elsewhere.[3e] Additional pertinent information is presented in table 3.

Electrocardiograms were available as early as the tenth day of the streptococcic illness in 6 cases and were already abnormal at that time

TABLE 3.—*Poststreptococcic Carditis: Clinical and Laboratory Data*

Case No.	Infecting Type	Erythrocyte Sedimentation Rate *					Electrocardiogram			
		First	Second	Third	Fourth	Day First Normal	Day First Done	Day First Ab-normal	Duration of Abnor-mality, Days	Key No.†
34	30	77/2	56/15	30/21	84/28	Over 29	7	7	Over 21	8
35	36 and 6	27/1	39/9	35/14	31/24	Over 24	13	13	Over 88	19
36	17 and 1	75/3	48/14	20/21	35/34	Over 25	9	9	10	7
37	17 and 44	Not done	52/11	54/28	55/42	Over 42	28	28	Under 14	4
38	17 and 30	40/3	75/16	98/29	66/43	Over 50	11	29	7	15
39	46	96/3	90/15	27/42	23/41	Over 41	9	9	28	1
40	19	54/3	64/10	11/16	Not done	16	10	10	7	3
41	26	58/3	42/9	56/32	31/44	Over 44	13	32	Over 12	6
42	36	26/3	12/9	Not done	87/40	Over 40	9	40	Unknown	18
43	44	14/3	11/10	25/30	Not done	Over 30	13	13	Under 11	20
44‡	36 and 1	36/3	13/8	22/22	Not done	Over 22	8	8	Under 14	

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which the test was done.
† Refers to number of the case under which electrocardiograms were described in a previous paper.[3e]
‡ T waves in lead II were of low voltage; in lead III they were inverted.

in 5. They remained so for more than seven days in 4 and more than twenty-one days in 2. Either the electrocardiogram became abnormal later, or earlier studies were not done on the other patients.

The erythrocyte sedimentation rate was invariably elevated at the time that evidence of carditis was first obtained, and it remained so for more than twenty days in 9 and more than forty days in 5 cases. All these men made a prompt recovery from the initial streptococcic infection and remained well. In none was clinical evidence of a continuing process elicited.

The electrocardiographic abnormalities were similar in nature to those present in patients with late fever or arthritis but were less decided and persistent than those noted in patients with involvement of the joints. Clinical signs of carditis were absent in all these patients.

Infection by a variety of serologic types of hemolytic streptococci preceded the development of carditis in this group. Bacteriologic evidence of reinfection by a new type was secured in 5 cases. In 3 this event was not associated with the development of the cardiac abnormality, but in 2 (cases 37 and 38) the relationship between the time of reinfection and the first appearance of an abnormal electrocardiogram was such as to indicate that the two occurrences were causally related.

Summary.—Abnormal electrocardiograms indicating the presence of carditis were discovered in men convalescent from hemolytic streptococcic sore throat who presented no clinical evidence of a continuing pathologic process. The erythrocyte sedimentation rate was elevated in all cases and usually remained so for three or more weeks.

LATE LYMPHADENITIS

Late lymphadenitis appearing during convalescence from hemolytic streptococcic sore throat has been regarded as a nonsuppurative complication of this disease. This concept was only partially correct as an explanation for the phenomenon in this group of patients. In certain cases it was difficult to be certain that a delayed extension of the suppurative process to the neighboring cervical glands had not occurred. In other patients, reinfection by a new type of hemolytic streptococcus during the convalescent period was associated with the development of tender adenitis in the anterior cervical region in the absence of pharyngeal signs which would have suggested that a new infection had occurred. This mechanism was positively identified as the cause in 7 examples of late adenitis, 5 as the result of reinfection during the food-borne epidemic in the hospital.[6] It was probably operative in cases 21 and 58 described in this paper.

There were 8 cases in which it was possible that nonsuppurative late lymphadenitis had supervened, since extensive bacteriologic investigation failed to reveal evidence of reinfection and the time of onset suggested that direct extension from the throat was improbable. The essential data are presented in table 4.

Adenitis was cervical in 7 cases and appeared from five to fifty days after the onset of the initial streptococcic infection. Glandular involvement was severe in 3 and moderately severe in the remaining cases. Abdominal pain began on the ninth poststreptococcic day in 1 man, and it continued for seven days. Physical examination of the abdomen revealed diffuse tenderness. It was believed that this episode was the result of abdominal lymphadenitis.

Fever accompanied the adenitis in 6 cases. The erythrocyte sedimentation rate was normal in 4 and only moderately elevated in 2 other patients during the period when lymphadenitis was extreme. In 3 other patients, a rapid erythrocyte sedimentation rate was observed at this

TABLE 4.—*Poststreptococcic Adenitis: Clinical and Laboratory Data*

Case No.	Infecting Type	Adenitis				Late Fever			Erythrocyte Sedimentation Rate *					Serial Electrocardiograms
		Day of Onset	Duration Days	Severity of Adenitis	Site of Adenitis	Day of Onset	Duration Days	Maximum Temperature, F.	First	Second	Third	Fourth	Day First Normal	
45	17	5	6	Severe	Cervical lymph glands	5	4	103.0	18/3	21/9	8/14	8/23	14	Normal
46	3	20	13	Moderately severe	Cervical lymph glands	Afebrile	Afebrile	98.6	14/2	6/8	3/13	2/33	2	Normal
47	17	50	5	Moderately severe	Cervical lymph glands	49	4	101.0	64/3	8/11	2/26	27/51	11	Not done
48	19	9	7	Severe	Abdominal lymph glands	10	6	101.0	Not done		42/18	Not done	Unknown	Not done
49	17	8	4	Moderately severe	Cervical lymph glands	5	5	100.0	10/3	15/10	3/19	Not done	3	Not done
50	Untypable and 26	Unknown		Moderately severe	Cervical lymph glands	Afebrile	Afebrile	98.6	39/3	35/8	40/19	43/28	40	Normal
51	Untypable	21	11	Extremely severe	Cervical lymph glands	23	9	102.0	22/3	13/11	6/24	3/36	8	Normal
52†	Untypable and 46	..	..	....	Cervical lymph glands									

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which the test was done.
† Data on this case are given in the text.

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time.   Serial electrocardiograms were obtained for 5 of these patients and were always normal.

Infection by no particular serologic type of streptococcus was likely to lead to the development of late adenitis.   Bacteriologic evidence of reinfection in 2 cases by an untypable strain was obtained, but the new organism was first isolated from the throat at such a time as to preclude its involvement in the process.

One case of late adenitis which presented many unusual features will be illustrated and described.
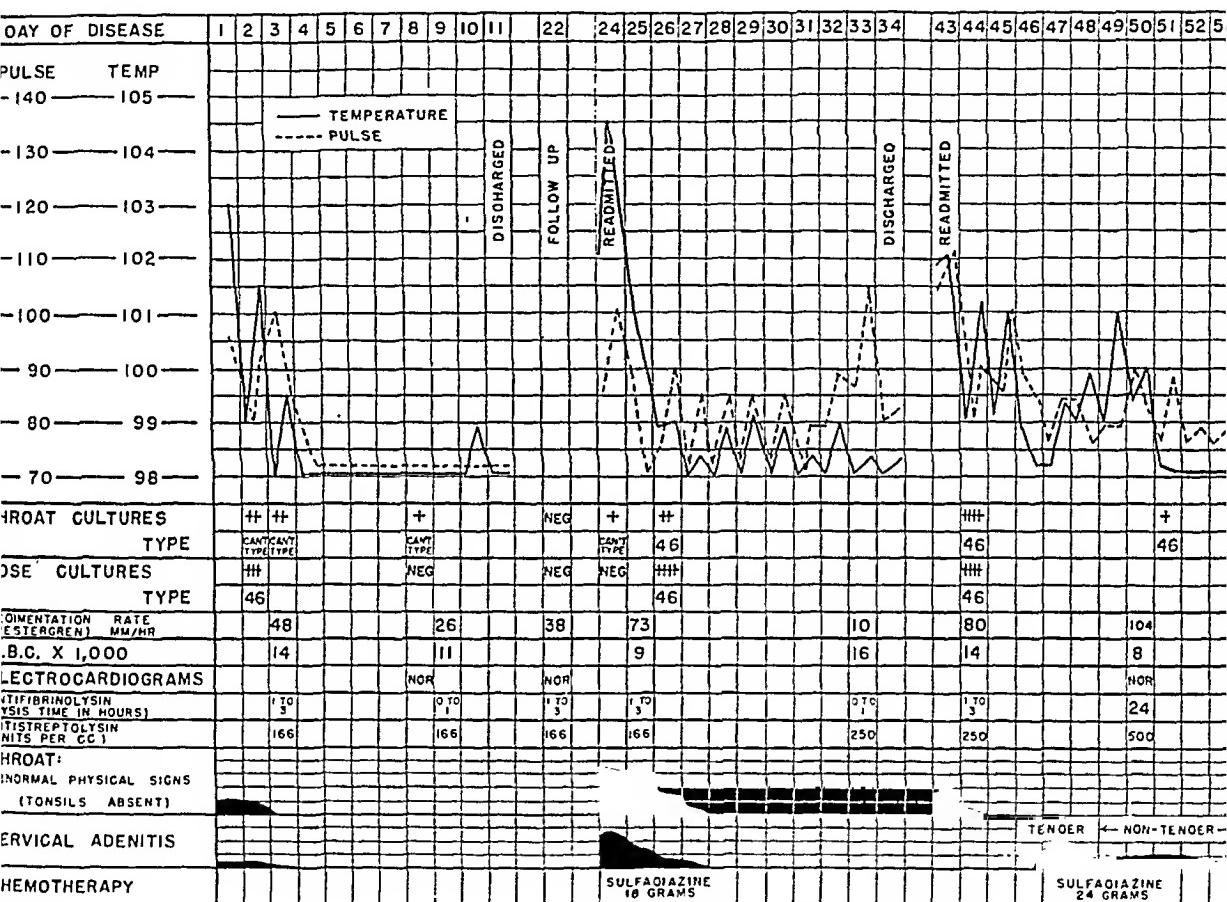
Chart 8.—Two episodes of poststreptococcic fever associated with cervical adenitis were seen in L. F. D., aged 24.

CASE 52 (chart 8).—A 24 year old man was admitted to the hospital on the first day of a moderately severe respiratory illness associated with few abnormal physical signs in the throat.   Anteriorly, tender cervical adenitis was present but minimal.   The erythrocyte sedimentation rate was elevated, and leukocytosis was discovered.   Large numbers of untypable group A hemolytic streptococci were recovered fron. the pharynx and organisms of type 46 from the nose.   The patient recovered promptly from this illness, but when he was seen in follow-up on the twenty-second day the erythrocyte sedimentation rate was still abnormal.   No hemolytic streptococci were isolated from materials obtained from the nose or throat.

Two days later he reentered the hospital, suffering from another severe respiratory illness. On this occasion the throat was fiery red, exudate was present on the tonsillar tags and there were large tender glands in the anterior cervical region. Moderately severe gingivitis was also observed. Untypable hemolytic streptococci were present in the throat and organisms of type 46 in both nose and throat. The erythrocyte sedimentation rate was decidedly elevated. Sulfadiazine was administered, and he again recovered promptly.

Another febrile illness supervened on the forty-third day. On this occasion the throat was approximately normal, and there was no cervical adenitis until the fifth day in the hospital, when an extremely large and tender gland appeared on the right. The erythrocyte sedimentation rate, which had been 80 mm. per hour on the patient's admission, became more rapid and had not returned to normal by the time of his discharge. Large numbers of type 46 streptococci were present in the nose and throat. Recovery from the last illness occurred within ten days. Sulfadiazine was administered but was used too late to have been of value. A few electrocardiograms were obtained and were normal.

Comment.—The interpretation of the clinical course in this case is difficult. Three distinct febrile episodes were observed. Type 46 hemolytic streptococci were recovered from the upper air passages on all three and untypable organisms on the first two occasions. The most probable explanation of this sequence of events appears to require that the first illness be regarded as an initial hemolytic streptococcic sore throat and that the second be regarded as an instance of relapse, with recurrence of abnormal physical signs in the throat and adenitis. The last illness may be regarded as a nonsuppurative complication, with fever, extremely rapid erythrocyte sedimentation rate and late adenitis but with no local signs in the throat.

Summary.—Tender cervical and, probably, abdominal lymphadenitis may appear during convalescence from hemolytic streptococcic sore throat. This may be the result of delayed extension of suppuration from the pharynx or of reinfection by a new type of Streptococcus. In other cases it is probable that another, perhaps nonsuppurative, process is involved. Late lymphadenitis was somewhat different from other manifestations of the poststreptococcic state, as observed during this study, since it was frequently associated with a normal erythrocyte sedimentation rate and evidence of carditis was never discovered by electrocardiographic examination.

PNEUMONIA

In 3 men an illness associated with pneumonitis developed while they were convalescent from hemolytic streptococcic sore throat. Because the cases are of unusual interest all will be described and illustrated.

CASE 53 (chart 9).—A 23 year old man was admitted to the hospital on the second day of a moderately severe hemolytic streptococcic sore throat. Organisms of types 19 and 24 were isolated from the throat. He was clinically well within four days and was discharged on the ninth day, having received 10 Gm. of sodium salicylate daily. The erythrocyte sedimentation rate increased while he was hospitalized and after discharge. On the twenty-third day he returned to the outpatient clinic. At this time he felt ill and exhibited a little fever, the erythrocyte

sedimentation rate was 89 mm. per hour and the electrocardiogram was abnormal, the T waves being inverted in the standard leads (case 24 [8e]). Higher temperature appeared on the next day, and he felt extremely ill.

The physical examination revealed nothing remarkable except for the presence of fine rales posteriorly over the lower part of the chest. A roentgenologic examination of the lungs four days later revealed the presence of a diffuse increase of the bronchial markings in the lower lobes of both lungs, similar to that often observed in primary atypical pneumonia. The leukocyte count was 15,000 per cubic centimeter, and the erythrocyte sedimentation rate was 107 mm. per hour on the fourth day in the hospital. An electrocardiogram at this time showed a
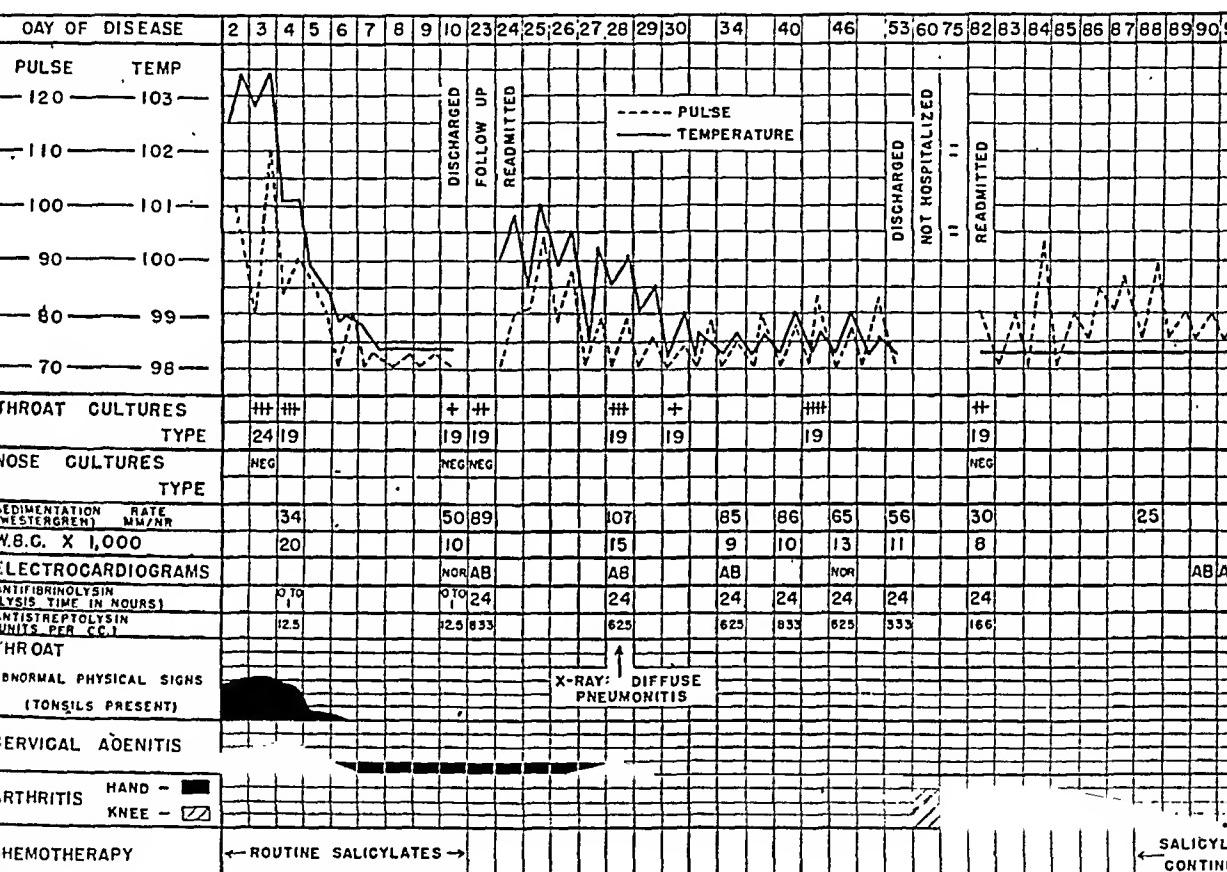
Chart 9.—J. D. E., aged 23, had poststreptococcic pneumonitis associated with carditis and followed by the development of arthritis.

prolongation of the P-R interval to 0.28 second. The T waves in all leads were isoelectric.

The patient's clinical recovery was complete in ten days, and the electrocardiogram returned to normal, but the erythrocyte sedimentation rate was 53 mm. per hour on the thirtieth day after the onset of the poststreptococcic fever. About three weeks later arthritis, associated with a rapid erythrocyte sedimentation rate but no fever, became manifest, and a prolongation of the P-R interval to 0.24 second was demonstrated. His symptoms subsided promptly after the administration of large amounts of sodium salicylate. Complete recovery had not occurred by the one hundred and third day, but no signs of valvular cardiac disease had appeared.

Comment.—This case demonstrates an example of fever and diffuse pneumonitis, associated with leukocytosis, a rapid erythrocyte sedimentation rate and abnormal electrocardiogram, following hemolytic streptococcic sore throat. A true latent period was absent. Later, typical mild rheumatic fever with carditis developed.

CASE 54 (chart 10).—A 21 year old man was admitted to the hospital on the second day of moderately severe sore throat caused by type 19 hemolytic streptococci, from which he recovered promptly without specific therapy. Pain in the left part of the chest and fever appeared on the fifth day. No abnormalities were discovered by physical or roentgenologic examination of the chest at that time. A pronounced leukocytosis was discovered on the eleventh day, which declined

DAY OF DISEASE	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32		37	6?
PULSE / TEMPERATURE (graph)																																TO CONVALESCENT BARRACKS	FOLLOW UP	FOLLOW UP
THROAT CULTURES	+++	+++								NEG		+++	+++				+++							+							+++			
TYPE	19	19										19	19				19							19							19			
NOSE CULTURES	+++									+																					NEG			
TYPE	19									19																								
SEDIMENTATION RATE (WESTERGREN) MM/HR		55									30						41							68							14		40	3
W.B.C. X 1,000		26								41	33			32			24							17							15		10	9
ELECTROCARDIOGRAMS												NOR																					NOR	
ANTIFIBRINOLYSIN (LYSIS TIME IN HOURS)		1 TO 3									24						24							24							24		24	
ANTISTREPTOLYSIN (UNITS PER CC)		500									833						1250							833							833		833	
THROAT ABNORMAL PHYSICAL SIGNS (TONSILS PRESENT)																																		
ADENITIS																																		
MISCELLANEOUS			CHEST PLATE NORMAL					X-RAY SHOWS SMALL AREAS OF PNEUMONITIS LEFT LUNG																									
		LEFT CHEST PAIN →																																

Chart 10.—R. E. C., aged 21, had poststreptococcic pneumonitis associated with an unusual degree of leukocytosis.

gradually but was still present on the thirty-second day. A roentgenologic examination of the chest on the twelfth day demonstrated patchy pneumonitis of the upper lobe of the left lung. He was essentially afebrile by the ninth day and remained so, but severe malaise persisted for more than four weeks and the erythrocyte sedimentation rate was still exceedingly rapid on the thirty-seventh day. Tachycardia was frequently observed during this period. Electrocardiographic study was inadequate.

Comment.—An example of pneumonitis associated with an unusual degree of leukocytosis and minimal fever following hemolytic streptococcic sore throat is here illustrated. Malaise persisted, and the erythrocyte sedimentation rate remained elevated for more than four weeks.

CASE 55 (chart 11).—A 19 year old youth was admitted to the hospital on the first day of an extremely severe sore throat caused by type 36 hemolytic streptococci, which was inadequately treated with penicillin. A clinical relapse followed the withdrawal of this agent. After this event he failed to become afebrile, felt ill and had pain in the chest, cough and severe headaches. The leukocyte count and erythrocyte sedimentation rates remained elevated. Repeated physical examination and roentgenologic studies of the chest failed to reveal abnormalities which would explain the prolonged disability.

The erythrocyte sedimentation rate had returned toward normal and he had clinically improved by the twenty-ninth day, and he was discharged a few days later, only to return on the thirty-sixth day. At that time fever and malaise were prominent, but the physical examination revealed nothing remarkable except for moderate redness and edema of the pharyngeal tissues. The erythrocyte sedimentation rate was abnormally rapid, but there was no leukocytosis. Hemolytic streptococci of two types, 36 and 17, were recovered from the nose and throat. Roentgenologic examination of the chest revealed patchy infiltration of the lower lobe of the left lung. He improved clinically and was afebrile on the fourth day in the hospital. Forty-eight hours later there was an abrupt rise in temperature, associated with the appearance of pain over the left part of the chest posteriorly. Physical examination of the lungs revealed no abnormalities, but roentgenologic study demonstrated diffuse pneumonitis involving most of the lower lobe of the left lung. The character and distribution of the observed lesions were similar to those seen in cases of primary atypical pneumonia. The erythrocyte sedimentation rate became more rapid, and leukocytosis developed. Pneumococci and hemolytic streptococci were not recovered from the sputum.

The temperature returned to normal coincident with the administration of sulfadiazine, but the patient failed to make a complete recovery. Malaise persisted for several weeks, and the erythrocyte sedimentation rate was still abnormally rapid eighty-three days after the onset of the initial sore throat and forty-seven days after his second admission to the hospital.

Electrocardiograms were obtained on several occasions and were always normal.

Comment.—In this case, prolonged unexplained fever followed hemolytic streptococcic sore throat. Later, a type of Streptococcus different from that causing the initial illness appeared in the throat. This event was closely associated with the reappearance of fever and of pneumonitis, from which he recovered extremely slowly, the erythrocyte sedimentation rate being abnormally rapid more than six weeks later.

Summary.—Roentgenologic evidence of patchy pneumonitis was obtained for 3 men in whom poststreptococcic febrile illness developed. The involvement of the lungs was associated in every case with leukocytosis—in 1 case of an extreme degree—and a greatly elevated erythrocyte sedimentation rate. Electrocardiographic evidence of carditis was present in 1 case. Pneumococci were not present in the sputums of these patients, and hemolytic streptococci were recovered in only small numbers.

Recovery from the acute febrile disease occurred promptly, and the lungs cleared rapidly but the erythrocyte sedimentation rate remained abnormally rapid for more than four weeks in all cases. Arthritis developed approximately one month after the onset of pneumonia in 1 man
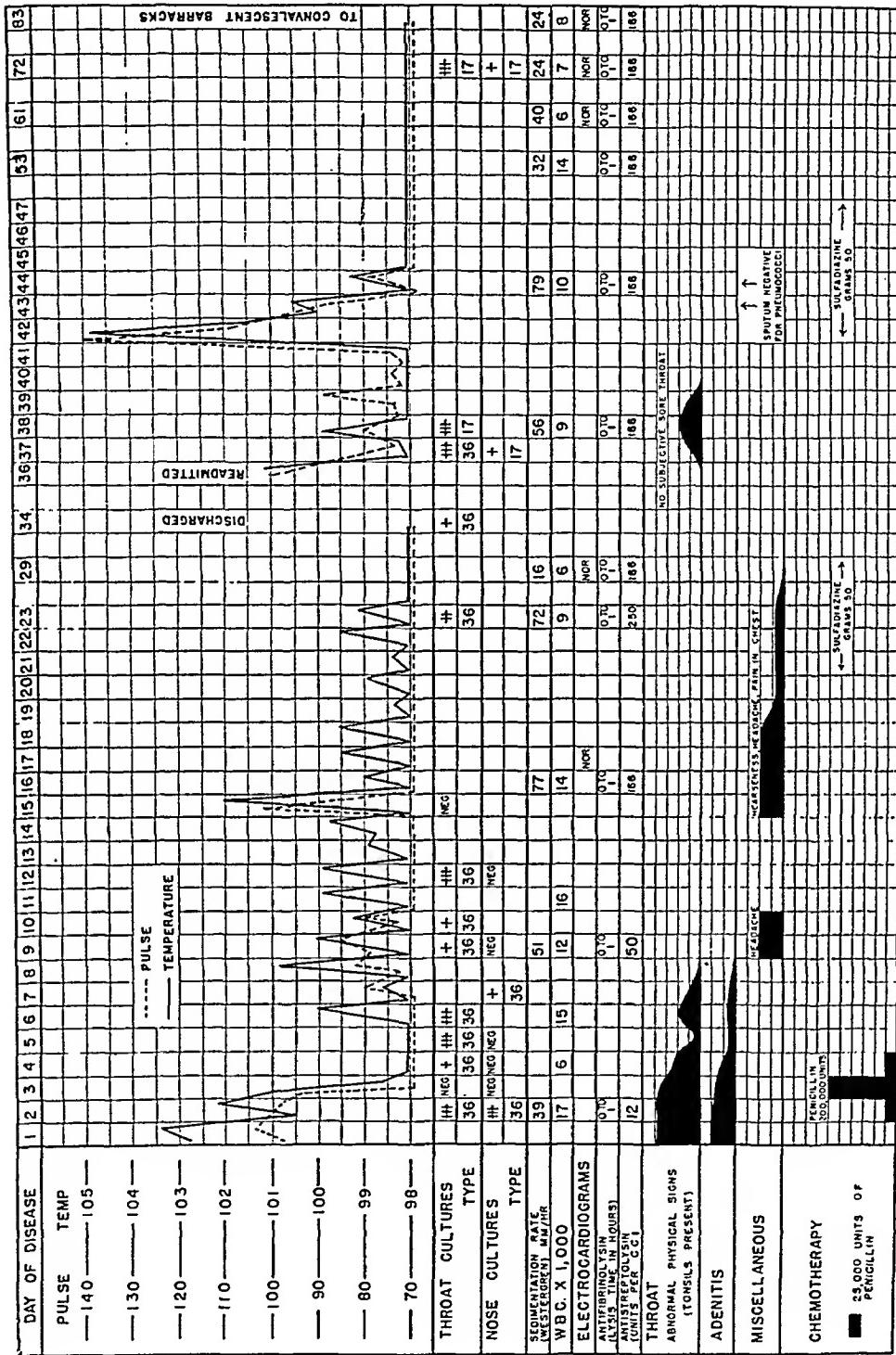
Chart 11.—Poststreptococcic pneumonitis following reinfection by a new serologic type of hemolytic streptococcus was observed in C. E. B., aged 19.

and was accompanied with a recrudescence of the electrocardiographic signs of carditis.

PERSISTENTLY RAPID ERYTHROCYTE SEDIMENTATION RATE

The erythrocyte sedimentation rate remained abnormally elevated for more than three weeks in 10 cases in which no evidence of a suppurative or nonsuppurative continuing disease could be discovered by clinical examination. The essential data are presented in table 5. In

TABLE 5.—*Persistent Poststreptococcic Prolongation of the Erythrocyte Sedimentation Rate: Clinical and Laboratory Observations*

Case No.	Infecting Type	Duration of Initial Fever	Erythrocyte Sedimentation Rate *				Day First Normal	Serial Electro-cardiograms
			First	Second	Third	Fourth		
58	Described and illustrated							
59	Untypable and 17	2	61/3	32/9	37/22	Not done	Over 22	Normal
60	36	4	30/3	Not done	27/24	Not done	Over 24	Not done
61	36	2	34/2	Not done	65/26	Not done	39	Not done
62	17	6	9/3	25/9	21/15	25/24	Over 24	Not done
63	3	1	22/4	9/10	30/23	Not done	Over 23	Normal
64	3	2	21/3	9/10	Not done	28/49	Over 49	Normal
65	3	3	29/3	22/9	25/22	Not done	Over 22	Normal
66	1 and 12	2	55/3	81/9	46/18	46/28	40	Normal
67	Untypable	3	35/2	32/8	29/22	Not done	Over 22	Normal

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which the test was done.

9 cases the erythrocyte sedimentation rate after three or four weeks was approximately as rapid as that observed initially or had increased. Serial electrocardiograms were obtained in 6 of these cases and were normal.

The course of the illness in 1 of these men is of particular interest and will be illustrated and described.

CASE 58 (chart 12).—An 18 year old youth was admitted to the hospital on the first day of a severe hemolytic streptococcic sore throat. Organisms of type 3 and of type 46 were isolated from the nose and throat. A prompt recovery was followed by an uneventful convalescence for a period of two weeks.

Severe tender adenitis of the anterior cervical region appeared on the seventeenth day, in association with a sharp rise in temperature and increase in the erythrocyte sedimentation rate and leukocyte count. The pharynx was approximateley normal on physical examination. This complication might have been regarded as nonsuppurative, but type 17 streptococci were now present in the throat, and it seemed clear that a reinfection had occurred.

Recovery from this disorder occurred quickly, and the patient returned to a state of full health. The erythrocyte sedimentation rate, however, remained extremely rapid for more than two months, having been 92 mm. per hour on the thirty-first day and 49 mm. per hour on the sixty-second day. Serial electrocardiograms were obtained between the tenth and thirty-ninth days and were normal.

Comment.—This case is an example of reinfection by a new type complicating convalescence from a hemolytic streptococcic sore throat and mimicking late non-suppurative adenitis. The second infection was followed by a prompt return of a sense of well-being, but a continuing reaction of the tissue persisted for more than six weeks.

Summary.—The erythrocyte sedimentation rate remained abnormally rapid for three or more weeks in certain cases in which clinical evidence of a suppurative process as a cause for the prolonged reaction of the tissue was not obtained. Clinical and electrocardiographic signs indicating the presence of a continuing illness were absent.

DAY OF DISEASE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	25	27	31	35	39	43	50	6
THROAT CULTURES		+++	+	+									+				+	+++	+++					+					
TYPE		3	46	46									46				17	46	17					17					
NOSE CULTURES		+++											NEG				NEG	++	+++										
TYPE		3																46	46										
SEDIMENTATION RATE (WESTERGREN) MM/HR		56								65					44				91			102	92					65	4
W.B.C. X 1,000		10								16					17				18			19	15		15			6	8
ELECTROCARDIOGRAMS										NOR					NOR				NOR			NOR	NOR		NOR				
ANTIFIBRINOLYSIN (LYSIS TIME IN HOURS)		0 TO 1								1 TO 3					0 TO 1				0 TO 1			8 TO 24	24		24			24	8 T 24
ANTISTREPTOLYSIN (UNITS PER CC)		166								333					833				1,250			2,500	3,300		5,000			1,250	125
THROAT: ABNORMAL PHYSICAL SIGNS (TONSILS PRESENT)																													
ADENITIS																													

Chart 12.—Persistent elevation of the erythrocyte sedimentation rate following infection and reinfection by different types of hemolytic streptococci in A. S., aged 18.

PURPURA

Nonthrombopenic purpura followed hemolytic streptococcic sore throat in 2 cases, making its appearance in 1 on the ninth and in the other on the thirty-first day after the onset of the respiratory infection. The hemorrhagic areas were confined to the feet and legs in both cases. Sulfadiazine had been administered to 1 man during the four days preceding the onset of the purpura and in the other twenty-six days before. Prompt and uneventful recovery occurred in both cases.

It is impossible to determine whether the hemorrhagic disease in these cases was the result of the antecedent streptococcic sore throat, of the administration of sulfonamide drugs or of exposure to some unknown toxic agent.

GLOMERULONEPHRITIS

Clinically recognizable glomerulonephritis did not follow in any of the cases of hemolytic streptococcic sore throat during this study. Detailed serial examinations of urine, suitable for the detection of minor degrees of albuminuria or hematuria, were not performed.

PROLONGED INITIAL FEVER

A prolonged severe febrile illness of ten or more days' duration, which could not be explained on the basis of a suppurative complication, accompanied the initial phase in 5 cases of hemolytic streptococcic sore throat. The essential information in regard to these men is presented in table 6. The erythrocyte sedimentation rate was always extremely rapid during this febrile period, and electrocardiographic abnormalities were discovered in 4 cases. Evidence of carditis persisted for more than seven days in 4; and more than twenty days in 2 cases. It consisted in prolongation of conduction time in 3 cases, which was associated with changes in the T waves in 1, and the latter sign alone was present in 1 case.

The administration of sulfadiazine was followed by a termination of the febrile illness in only 1 of the 2 cases in which this drug was used. Two hundred thousand units of penicillin, administered in thirty-six hours, did not alter the course in another case. Salicylates were not given to any of these patients.

Two of these 5 men were followed for an insufficiently long period to define the natural history of the disease. The erythrocyte sedimentation rate, but not the electrocardiogram, had returned to normal by the twenty-first day in 1, the thirty-second day in another and the forty-seventh day in a third. The erythrocyte sedimentation rate remained rapid at the last examination of the other 2 patients on the twenty-eighth and thirty-sixth days of their illness. Abnormalities of the electrocardiogram also were demonstrable at that time in 1 in whom evidence of carditis had been previously discovered.

One of these cases of prolonged initial fever will be described and illustrated.

CASE 70 (chart 13).—A 34 year old man was admitted to the hospital on the first day of a severe sore throat caused by type 17 hemolytic streptococci. There were definite signs of maxillary sinusitis. No antibacterial therapy was instituted. He improved somewhat but remained febrile until the tenth day, when there was a sharp rise in temperature accompanied with a shaking chill. At that time, the physical examination revealed no definite abnormalities, and the signs of infection of the paranasal sinuses had disappeared. The culture of the blood was sterile.

Sulfadiazine was administered, and he rapidly became afebrile and remained so. He felt well by the twenty-eighth day, and the erythrocyte sedimentation rate

was declining. Electrocardiograms (case 13 [3e]) obtained at frequent intervals between the ninth and thirty-third days were always abnormal. The P-R interval increased from 0.20 second on the ninth day to 0.24 second on the nineteenth day and then decreased to 0.19 second on the thirty-third day. The T waves were always sharply inverted in leads I and II.

Comment.—This is an example of prolonged initial fever, complicating hemolytic streptococcic sore throat, which was not readily explained on the basis of
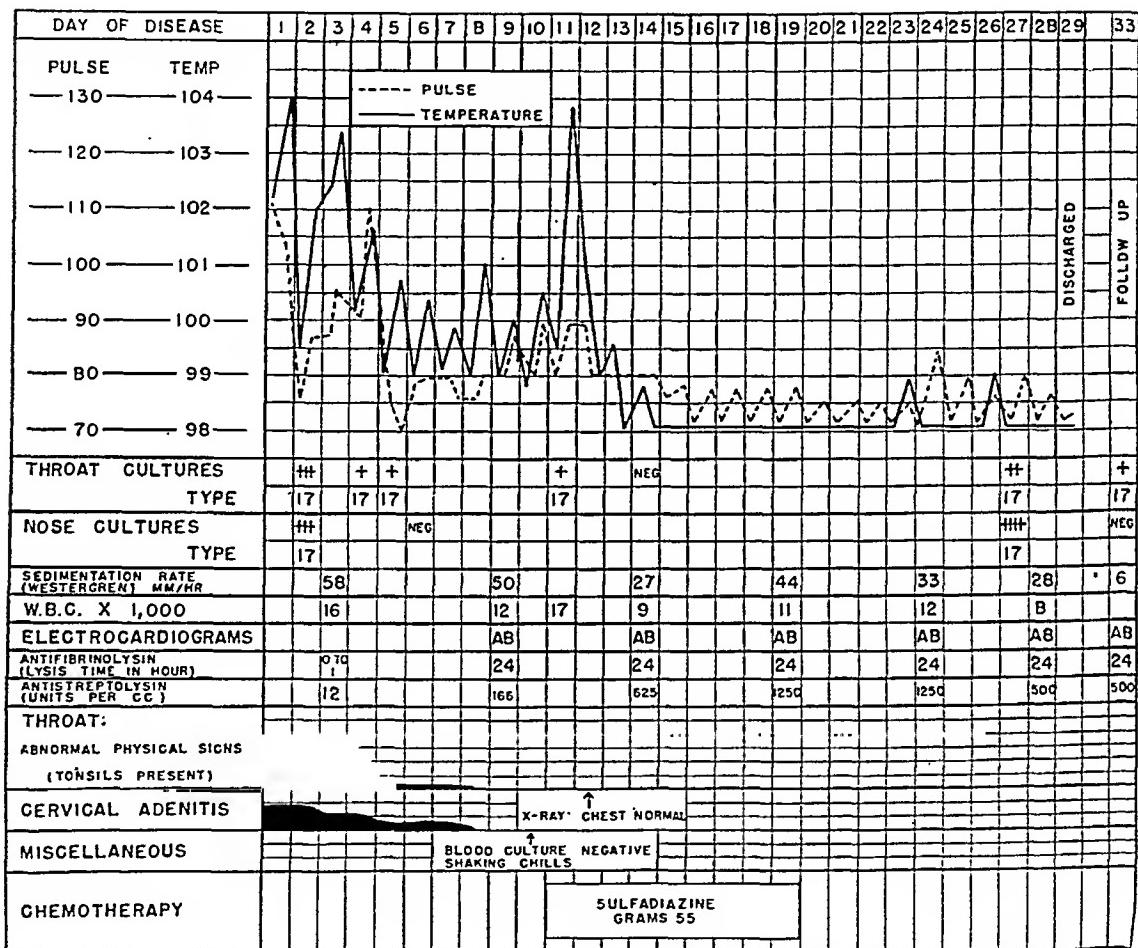
Chart 13.—Hemolytic streptococcic sore throat complicated by a prolonged initial fever and electrocardiographic evidence of carditis were seen in F. D. A., aged 34.

demonstrable continuing suppuration. Electrocardiographic evidence of carditis was present on the ninth day and persisted through the thirty-third day.

Summary.—Prolonged initial fever, not adequately explained on the basis of a diagnosable suppurative complication, was observed in 5 cases of hemolytic streptococcic sore throat. Electrocardiographic evidence of carditis was obtained for 4 of these cases. Complete recovery, with return of the erythrocyte sedimentation rate and electrocardiogram to normal, was delayed in certain cases.

TABLE 6.—*Prolonged Initial Streptococcic Fever: Clinical and Laboratory Data*

Case No.	Initial Fever			Erythrocyte Sedimentation Rate *					Electrocardiogram			
	Infecting Type	Maximum Temperature, F.	Duration, Days	First	Second	Third	Fourth	Day First Normal	Day First Done	Day First Abnormal	Duration of Abnormality, Days	Key No.†
68	30	103.0	14	70/4	54/15	36/25	Not done	Over 25	10	Normal	Normal	0
69 ‡	46	103.0	11	37/2	49/8	33/14	7/17	Over 14	8	8	Over 7	13
70	17	103.0	13	58/3	50/9	44/10	28/28	33	9	9	Over 28	2
71	17 and 36	103.0	10	23/3	75/11	5/32	Not done	Over 12	12	12	Over 20	
72	46	103.0	10	53/3	38/12	21/16	5/21	21	14	14	Over 8	11

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which the test was done.
† Refers to the number of the case under which electrocardiograms were described in a previous paper.[²⁶]
‡ T waves of low voltage in leads I and II on first two examinatións (on the eighth and fifteenth days). On the forty-seventh day the T waves were normal.

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THERAPY

A number of therapeutic regimens were utilized in the treatment of the initial streptococcic sore throat in this group of patients. These have been described in detail elsewhere [3c] but may be summarized. Penicillin was administered intramuscularly in a short course (200,000 to 400,000 units in thirty-two hours), in a long course (500,000 to 1,000,000 units in eighty hours) and in a short course followed by sulfadiazine (an average of 39 Gm. in six and a half days). Ten grams of sodium salicylate per day was administered to another group from approximately the second to the tenth day of illness. Only symptomatic therapy was used in the management of 63.5 per cent of the patients.

Data pertinent to the evaluation of the effect of these several therapeutic regimens on the subsequent development of nonsuppurative complications after hemolytic streptococcic sore throat are presented in table 7.

TABLE 7.—*Effect of Therapy on the Development of Poststreptococcic Complications*

Therapy	No. of Cases	Arthritis		Late Fever		Carditis		Late Adenitis		Total of Arthritis, Late Fever, Carditis [*]	
		No.	%	No.	%	No.	%	No.	%	No.	%
Penicillin, short course..........	20	1	5.0	1	5.0	1	5.0	1	5.0	3	15.0
Penicillin, long course...........	13	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Penicillin and sulfadiazine......	28	4	14.3	2	7.1	3	10.7	1	3.0	9	32.1
Sulfadiazine.....................	37	1	2.7	1	2.7	1	2.7	0	0.0	3	8.1
Salicylates......................	27	0	0.0	2	7.4	1	3.7	0	0.0	3	11.1
None............................	217	13	6.0	8	3.7	5	2.3	6	2.8	26	12.0

[*] Three cases of poststreptococcic pneumonitis have not been included. One patient received a short course of penicillin and another sodium salicylate during the initial illness.

All the patients were not followed for identical periods or studied in comparable detail, and the number of cases in each chemotherapeutic category is small. Furthermore, chemotherapy was usually reserved for the most severely ill men. It was believed, however, that this information was of sufficient interest to deserve exhibition.

Particular emphasis is placed on the frequency of occurrence of arthritis, late fever and carditis, since these are almost certainly varying manifestations of a single pathologic process. The incidence of these three nonsuppurative complications was similar among untreated patients and those who received a short course of penicillin, sulfadiazine alone or sodium salicylate but was much higher in the group in which a short course of penicillin was followed by administration of sulfadiazine. No late complications of any kind occurred in patients who had received the long course of penicillin.

Summary.—The effect of antibacterial and salicylate chemotherapy of hemolytic streptococcic sore throat on the subsequent development of nonsuppurative complications has been analyzed. The treated and

untreated patients are not strictly comparable as to the nature and severity of the initial illness, and the number of cases in each category is too small to permit reliable analysis.

It is not believed that any conclusions whatever can be drawn from these data. They are presented for the information of other investigators. Nonsuppurative complications were absent in the group receiving 500,000 to 1,000,000 units of penicillin in eighty hours. It would, therefore, seem desirable to continue the study of the effect of the administration of this chemical to human beings infected by hemolytic streptococci to determine whether its use in such cases in large amounts will decrease the frequency of occurrence of the serious late nonsuppurative complications.

COMMENT

A large number of cases of sore throat caused by group A hemolytic streptococci in young adults was studied. Complete and uneventful recovery occurred frequently, but convalescence in many instances was marred by the development of a complication. Often this was the result of local suppuration, but in approximately 20 per cent of all cases a disorder supervened which could not be demonstrated to be the result of the local extension of the initial process in the throat or the invasion of remote tissues by hemolytic streptococci. A similar sequence of events has been observed by other investigators.[7]

Arthritis of varying degrees of severity was the commonest type of late nonsuppurative complication. Involvement of the joints was associated in certain cases with fever and clinical and/or electrocardiographic evidence indicating the presence of carditis. Such cases were then indistinguishable from cases of classic rheumatic fever. Fever or carditis often was absent. Demonstrable involvement of the heart was more likely to occur in febrile patients.

The febrile and arthritic phases of this poststreptococcic disorder were nearly always terminated by the administration of salicylates, but final recovery was delayed, the erythrocyte sedimentation rate having remained elevated in every case for more than thirty days.

The convalescence of another group of patients nearly as large as that just described was complicated by a recrudescence of fever, after a period of normal temperature following the initial respiratory illness, of from five to nineteen days in duration. Evidence of carditis in the form of abnormal electrocardiograms was discovered in more than one third of these cases. This febrile disease, except for the absence of involvement of the joints, closely resembled the arthritic poststreptococcic disorder just described, but there were important differences, as well

7. Watson, R. F.; Rothbard, S., and Swift, H. F.: The Relationship of Postscarlatinal Arthritis and Carditis to Rheumatic Fever, J. A. M. A. **128**:1145 (Aug. 18) 1945.

as similarities, between the two groups of cases. The complication appeared earlier, was less severe, as estimated by the degree of fever and the degree of abnormality of the erythrocyte sedimentation rate and electrocardiogram, and was of shorter duration if arthritis was absent.

Abnormalities of the electrocardiogram were discovered in another group of patients during convalescence from the initial streptococcic infection, in the absence of fever, arthritis or other clinical evidence of disease. The erythrocyte sedimentation rate was elevated in all these cases when evidence of carditis was first discovered, and usually it remained so for three or more weeks.

Involvement of the valves of the heart was not definitely recognized in any of the patients in the three categories just described during the relatively brief period of follow-up study that was available, nor was there clinical evidence of acute carditis in any except a few of the cases of arthritis. This may have been the result of the prolonged hospitalization of most of the patients during the period of intensive study. Others [8] have described cardiac pain, gallop rhythm, enlargement of the heart and collapse in similar patients subjected to more strenuous activity.

Three cases were studied that were of the greatest interest since a febrile disease associated with roentgenologic evidence of pneumonitis appeared during the poststreptococcic period. These cases would probably have been regarded as examples of primary atypical pneumonia if the initial streptococcic illness had not been observed and follow-up studies instituted. That this pneumonitis was a form of poststreptococcic nonsuppurative complication is strongly suggested by the following facts: 1. Pneumococci were absent from and hemolytic streptococci present in only small numbers in the sputum. 2. The clinical course of the disease was in no case that of ordinary hemolytic streptococcic suppurative pneumonia, since the disease was relatively mild and resolved promptly in all and without the use of chemotherapy in 2 cases. 3. The roentgenologic appearance of the lesion was not that usually presented by bacterial pneumonia. These observations indicate that pneumonitis in these men was not the result of direct invasion of the lung by hemolytic streptococci or by another organism. 4. The leukocytosis which was present in all would have been unusual in primary atypical pneumonia of probable virus origin, as would the exceedingly prolonged postpneumonic disability, with rapid erythrocyte sedimentation rate, which persisted for more than forty days in all cases.[9] 5. Definite abnormalities

8. Scherf, D.: Myocarditis Following Acute Tonsillitis, Bull. New York M. Coll. Flower & Fifth Ave. Hosp. 3:252, 1940. Weinstein, J.: "Atypical" Coronary Disease in Young People, Ann. Int. Med. 21:252, 1944.

9. Curnen, E. C.; Mirick, G. S.; Ziegler, J. E., Jr.; Thomas, L., and Horsfall, F. L., Jr.: Studies on Primary Atypical Pneumonia, Clinical Features and Results of Laboratory Investigations, J. Clin. Investigation 24:209, 1945.

of the electrocardiogram, identical with those observed in other post-streptococcic disorders, were discovered in 1 man during the course of the pneumonic disease. Such evidence of carditis has not been observed in pneumonia of the virus type.[9] 6. Arthritis appeared in the patient just described while he was convalescent from pneumonitis.

Pneumonitis has long been recognized as a part of the syndrome of "rheumatic fever."[10] It is suggested that these examples of non-arthritic poststreptococcic pneumonia are examples of a related nonsuppurative process. Similar conditions have been observed by others following hemolytic streptococcic sore throat in military personnel.[11] Examination of the records of cases on which other reports were based, in which electrocardiographic abnormalities during the course of atypical pneumonia were described, strongly suggests that these were examples of poststreptococcic pneumonitis.[12]

In addition to these patients in whom clinical or electrocardiographic evidence of a disease process was discovered following hemolytic streptococcic sore throat, there were a few patients in whom the only sign of a continuing reaction of the tissue was a persistently elevated erythrocyte sedimentation rate in the absence of a demonstrable suppurative complication.

All these disorders, with or without arthritis or carditis, which have been observed to follow hemolytic streptococcic infection are believed to be manifestations of the same pathologic process. Their relationship to one another and their pathogenesis, so far as it may be elucidated by the present study and an analysis of previously reported investigations, have been fully considered elsewhere.[3d] It was suggested that these late complications of streptococcic disease were not the result of direct invasion of the affected tissues by the etiologic agent but of a more complex mechanism. An immunologic reaction, which occurred in persons whose tissues had been sensitized to some fraction or product of the hemolytic streptococcus as the result of previous infection by this organism, was a probable explanation for these phenomena.

The suggestion was made that all these disorders which are initiated by hemolytic streptococcic infections be grouped together and be regarded

10. Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, Medicine 7:383, 1928. Jensen, C. R.: Nonsuppurative Poststreptococcic (Rheumatic Pneumonitis): Pathological Anatomy and Clinical Differentiation from Primary Atypical Pneumonia, Arch. Int. Med. 77:237 (March) 1946.

11. Plummer, N.; Duerschner, D. R.; Warren, H. D.; Rogliano, F. T., and Sloan, R. H.: Penicillin Therapy in Hemolytic Streptococcic Pharyngitis and Tonsillitis, J. A. M. A. 127:369 (Feb. 17) 1945.

12. (a) Finkelstein, D., and Klainer, M. J.: Pericarditis Associated with Primary Atypical Pneumonia, Am. Heart J. 28:385, 1944. (b) Fuller, C. C., and Quinlan, J. W.: Acute Pneumonitis and Pericarditis: Report of a Case, New England J. Med. 229:399, 1943.

as phases of the "poststreptococcic state." This concept states the essential streptococcic causation of rheumatic fever, adequately emphasizes nonarthritic poststreptococcic continuing disease as a potential cause of chronic valvular cardiac disease and simplifies the clinical consideration of the various manifestations of these conditions.

During the course of the investigation described here, certain other cases were observed in which complications followed streptococcic infection that were not clearly related to those enumerated here. Enlargement of the cervical lymph glands, with tenderness, developed in several men while convalescent from the initial infection. In certain cases this seemed to be caused by a delayed extension of the suppuration in the throat and in others was definitely the result of reinfection by a new type of hemolytic streptococcus. In the latter event, lymphadenitis appeared in the absence of the usual pharyngeal signs of streptococcic infection. There were a few patients in whom neither of these mechanisms could be established as the cause of late lymphadenitis and fever. The disease was, however, different from the other nonsuppurative complications described and may have another pathogenesis, because the erythrocyte sedimentation rate was usually normal during the height of the glandular involvement and later, and abnormalities of the electrocardiogram were never discovered.

Nonthrombocytopenic purpura, which may have been the result of the preceding streptococcic infection, occurred in 2 patients. A decision as to the cause of this complication cannot be made. Glomerulonephritis was not recognized as a sequel to hemolytic streptococcic infection during this study.

The initial sore throat was complicated by a prolonged febrile course, which could not be explained on the basis of any discovered continuing suppuration in 5 cases. Electrocardiographic abnormalities were present in 4 of these which were similar to those previously described in other cases included in this study. It may be that the prolonged disease in these cases was the result of hidden suppuration and that the alterations in the electrocardiogram were those which have been previously described in febrile persons.[18] It is not improbable that the early supervention of a nonsuppurative disorder similar to those described earlier had occurred, but this hypothesis cannot be definitely established.

Certain bacteriologic information obtained from study of the initiating streptococcic infection or infections has been included in the tables. The significance of these observations has been described and discussed elsewhere.[3d]

The treatment of the acute phase of hemolytic streptococcic sore throat by the administration of large amounts of sodium salicylate, a

13. Master, A. M., and Jaffe, H.: Electrocardiographic Evidence of Cardiac Involvement in Acute Disease, Proc. Soc. Exper. Biol. & Med. **31**:931, 1934.

short course of penicillin alone or followed by a sulfonamide compound or the use of the latter drug alone did not prevent the development of late nonsuppurative complications. Poststreptococcic disorders were not observed in a small group of men who received 500,000 to 1,000,000 units of penicillin in eighty hours, but these results are not convincing, since the number of patients so treated was small.

Hemolytic streptococcic sore throat in young adults is a serious disease, the course of which may be complicated by the development of nonsuppurative disorders of which arthritis, fever and carditis in various combinations are the most important manifestations. Their recognition and proper management is of the greatest importance, since they prolong the period of disability, do not respond to the usual antibacterial chemotherapy and may be followed by the development of chronic valvular cardiac disease.

Intensive investigation of the phenomena of the poststreptococcic state is imperative for the purpose of discovering the pathogenesis of these disorders, technics for their recognition and methods for their prevention and treatment.

CARDIAC FAILURE IN PENICILLIN–TREATED SUBACUTE BACTERIAL ENDOCARDITIS

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SINCE the advent of penicillin in the treatment of subacute bacterial endocarditis, it has become increasingly obvious that certain patients are being cured of the infection only to suffer cardiac failure later. Many reports of treatment with penicillin mention cases in which there were unsatisfactory results, not because the drug failed to eliminate the bacteria but because of subsequent deterioration of cardiac function.[1] Inasmuch as the infection occurs in persons who have more or less damaged hearts to begin with and who might therefore be expected at some time to show symptoms of myocardial weakness, it seems illogical to blame penicillin unless its use can be shown to have hastened cardiac insufficiency. Obviously the drug cannot be expected to repair damage already done either by the original cardiac disease or by the bacterial endocarditis; the question is whether penicillin is likely to promote destructive processes. The purpose of this study is to determine (a) the part, if any, which administration of penicillin plays in promoting or postponing cardiac failure and (b) the factors in the patient with subacute bacterial endocarditis which predispose him to cardiac failure even if his vegetations are sterilized.

A. THE PART PLAYED BY PENICILLIN THERAPY IN CARDIAC FAILURE

1. *The Incidence of Cardiac Failure in Untreated Patients.*—To evaluate the significance of cardiac insufficiency in penicillin-treated patients, it is necessary to appreciate the incidence of cardiac failure

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1. (a) Loewe, L.: The Combined Use of Anti-Infectives and Anticoagulants in the Treatment of Subacute Bacterial Endocarditis, Bull. New York Acad. Med. **21**:59, 1945. (b) Meads, M.; Harris, H. W., and Finland, M.: Treatment of Bacterial Endocarditis with Penicillin: Experiences at Boston City Hospital During 1944, New England J. Med. **232**:463, 1945. (c) Bloomfield, A. L.; Armstrong, C. D., and Kirby, W. M. M.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, J. Clin. Investigation **24**:251, 1945. (d) Bloomfield, A. L., and Halpern, R. M.: The Penicillin Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **129**:1135 (Dec. 22) 1945. (e) Favour, C. B.; Janeway, C. A.; Gibson, J. G., and Levine, S. A.: Progress in the Treatment of Subacute Bacterial Endocarditis, New England J. Med. **234**:71, 1946.

in untreated patients. In order to emphasize the fact that symptoms of cardiac failure are not essential for the diagnosis of early subacute bacterial endocarditis, most observers have greatly underrated their incidence and have considered that cardiac insufficiency does not play an appreciable part in the course of the disease, even though often present terminally. The stress has been on the greater importance of embolic phenomena, sepsis or toxemia, and cardiac failure is considered but a result of exhaustion. Sir Thomas Horder observed that decompensation is so unusual in endocarditis that "we do not regard it as a disease of the heart at all." [2] Libman wrote that myocardial weakness occurred late and then was of "the type due to fever, anemia, and general weakness." [3] The myocardial insufficiency that Thayer observed in one fourth of his patients he considered to be merely one of the features of a "grave septicemia." [4] Sir Thomas Lewis found congestive failure one of the chief causes of death but considered that "it is always terminal." [5] White said that "rarely is there enough additional damage to the heart from this infection to cause heart failure directly." [6] Buchbinder and Saphir, however, found clinical cardiac failure of two to eight weeks' duration in 45 per cent of their patients and decided chronic passive congestion of the viscera at autopsy in 30 per cent more.[7] They described the uniform finding in their patients of extensive myocardial lesions adequate to explain cardiac failure apart from the effects of vague toxemia. They concluded that cardiac failure occurs in subacute bacterial endocarditis more frequently than is generally recognized and that it may be of some standing and not a mere terminal event.

My associates and I have reviewed 55 unselected cases of subacute nonhemolytic streptococcic endocarditis which were studied in this clinic in the ten years preceding the use of penicillin. Forty of the patients were examined at autopsy in the department of pathology, 13 having been followed in our clinic and 27 elsewhere. Seven other patients were followed in this clinic until death but were not examined at autopsy, and 8 were hospitalized here temporarily but were not adequately followed.

2. Horder, T.: The Clinical Significance and Course of Subacute Bacterial Endocarditis, Brit. M. J. 2:301, 1920.

3. Libman, E.: The Clinical Features of Subacute Streptococcus Endocarditis, M. Clin. North America 2:117, 1918.

4. Thayer, W. S.: Observations on Rheumatic Pancarditis and Infective Endocarditis, Ann. Int. Med. 5:247, 1931.

5. Lewis, T.: Diseases of the Heart, New York, The Macmillan Company, 1937, p. 187.

6. White, P. D.: Heart Disease, New York, The Macmillan Company, 1944, p. 365.

7. Buchbinder, W. C., and Saphir, O.: Heart Failure in Subacute Bacterial Endocarditis, Arch. Int. Med. 64:336 (Aug.) 1939.

The results in the cases which came to autopsy are recorded in table 1. A total of 10 patients (25 per cent) died of congestive failure. Twelve more (30 per cent) had symptoms and signs of cardiac weakness, such as dyspnea, orthopnea, rales at the bases of the lungs, engorgement of the liver and dependent edema, although the immediate cause of death was noncardiac, such as an embolic accident, renal failure or pneumonia. The duration of symptoms was from a few days to several months. In at least 1 case, symptoms of definite cardiac insufficiency antedated the infection by several years. Ten other patients (25 per cent) had no clinical symptoms or signs of myocardial weakness but on pathologic examination showed chronic passive hyperemia of the lungs and liver. Only 8 (20 per cent) had no clinical or pathologic evidence of cardiac failure. Therefore 80 per cent had evidence of some degree of myocardial insufficiency at the time of death. These

TABLE 1.—*Incidence of Cardiac Failure in Forty Untreated Patients with Sub-acute Bacterial Endocarditis*

	Cases Followed in This Clinic	Cases Followed Elsewhere, Autopsy Here	Total	Per Cent
Cardiac failure the cause of death.....................	4	6	10	25
Cardiac failure present in some degree, but not the immediate cause of death............................	3	9	12	30
Pathologic but no clinical evidence of cardiac failure	3	7	10	25
No clinical or pathologic evidence of cardiac failure..	3	5	8	20

figures correspond to those of Buchbinder and Saphir. Of the 7 patients followed until death but not examined pathologically, 2 died of cardiac failure, 2 had suggestive signs and 3 were not known to have signs of cardiac failure. Of the 8 who were seen but not followed, 1 had definite failure of fairly long standing, 2 had signs of early decompensation and 5 had no definite evidence of failure when last seen.

2. *The Incidence of Cardiac Failure in Penicillin-Treated Patients.*— In our series of 25 patients who have been followed for three to twenty-five months after completion of penicillin therapy, varying degrees of cardiac insufficiency have occurred in about 30 per cent. Of this group, 18 are alive and 7 are dead. As shown in table 2, 2 died of sudden accidents, thought to be cardiac, during therapy, 4 died of progressive cardiac failure after otherwise successful therapy and 1 died of an unrelated condition fifteen months later. Of the 18 who are alive, 3 have had definite signs or symptoms of cardiac failure and 15 have fairly good to excellent cardiac reserve. When the 2 who died of sudden accidents during treatment are included, cardiac failure developed in a total of 9 (36 per cent). When the 2 who died before the infection could be shown to have been eliminated are excluded, cardiac failure

has developed in 7 of 23 patients (30.4 per cent) in spite of eradication of the bacteria. Four of these patients (17.4 per cent) have died, and 3 (13 per cent) are living but require digitalis and rigid restriction of activity. Sixteen (69.6 per cent), therefore, have thus far escaped cardiac failure.

It·may be concluded from these comparative studies that cardiac insufficiency is a potentially important complication in a large majority of untreated patients with subacute bacterial endocarditis and that as far as the group as a whole is concerned the use of penicillin postpones cardiac failure and reduces its incidence. Whether this is true in all individual cases is not settled by such statistics. As will be discussed

TABLE 2.—*Incidence of Cardiac Failure in Twenty-Five Patients with Subacute Bacterial Endocarditis Treated with Penicillin*

	Dead	Living	Per Cent of Whole Series	Per Cent of Those Cured of Infection
Sudden cardiac accident during treatment, before cure of infection	2	..	8	
Cardiac failure following otherwise successful treatment	4	3	28	30.4
No cardiac failure	1	15	64	69.6
Excellent cardiac reserve	..	7	28	30.4
Good cardiac reserve	1*	6	28	30.4
Fair cardiac reserve	..	2	8	8.7

.* Died of an unrelated condition.

later, it seems in some instances that absorption of valvular vegetations under the influence of penicillin may, by further distorting the valve, actually hasten cardiac failure.[1d] In contrast to these few cases, however, are the many young persons with little previous cardiac damage who would certainly suffer some degree of cardiac failure in the course of their endocarditis, to say nothing of the other hazards, were it not for penicillin. The impression that use of penicillin promotes cardiac failure is probably due to the fact that it rescues patients from death due to embolic accidents or generalized sepsis long enough for them to suffer insufficiency of an already damaged myocardium. In general, therefore, the use of penicillin unmasks, rather than promotes, cardiac decompensation.

B. FACTORS WHICH DETERMINE CARDIAC RESERVE AFTER PENICILLIN TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

In order to aid preservation of good cardiac function after eradication of active bacterial endocarditis, it is desirable to have clearly in mind the reasons why some persons go through the infection unscathed while others become invalids with cardiac disease. In this study we

Table 3.—*Relationship of Various Factors to Cardiac Reserve After Penicillin Treatment in Twenty-Five Cases of Subacute Bacterial Endocarditis*

Name	Age, Yr.	Type of Lesion of the Heart	Cardiac Reserve Before Treatment	Appearance of Heart in the Roentgenogram	Time Until Adequate Treatment, Mo.	Average Daily Temperature, C.	Bacteria per Cc.	Clinical Appearance	Cure After Treatment	Follow-Up Period, Mo.	Present Cardiac Reserve
1. L. C.	22	Congenital coarctation of aorta	Excellent	Large	3	38.8 (101.8 F.)	70	Good	Good	25	Excellent
2. E. G.	41	Mitral stenosis	Fair	Slightly large	3	39.0 (102.2 F.)	400	Poor	Good	3	Dead *
3. C. B.	34	Mitral stenosis	Fair	Slightly large	6	39.1 (102.3 F.)	Few	Poor	Poor	9	Dead *
4. M. T.	20	Aortic insufficiency	Excellent	Large	½	38.9 (102 F.)	25	Good	Good	24	Good
5. O. S.	53	Uncertain mitral disorder	Excellent	Normal	2	38.5 (101.3 F.)	25	Good	Good	23	Excellent
6. F. H.	50	Mitral stenosis	Fair	Slightly large	2	37.3 (99.1 F.)	40	Fair	Good	22	Poor
7. J. D.	64	Uncertain mitral disorder	Excellent	Normal	2	38.5 (101.3 F.)	25	Good	Good	22	Excellent
8. S. M.	18	Uncertain mitral disorder	Good	Slightly large	6	37.7 (99.8 F.)	8	Good	Good	21	Good
9. A. S.	64	Mitral stenosis	Good	Slightly large	2	38.5 (101.3 F.)	70	Good	Good	15	Good †
10. O. E.	29	Mitral stenosis	Poor	Large	1	39.3 (102.7 F.)	8	Poor	Good	12	Dead *
11. R. D.	23	Aortic insufficiency	Poor	Slightly large	3	39.8 (103.6 F.)	50	Poor	.....	::	Dead †
12. M. S.	22	Uncertain	Excellent	Normal	4	38.5 (101.3 F.)	100	Good	Good	18	Excellent
13. B. S.	23	Aortic insufficiency	Good	Large	5	38.9 (102 F.)	25	Fair	Good	17	Fair
14. V. T.	60	Aortic insufficiency; auricular fibrillation	Fair	Large	3	39.0 (102.2 F.)	80	Fair	.....	::	Dead ‡
15. R. L.	32	Aortic insufficiency	Good	Slightly large	2	38.0 (100.4 F.)	6	Good	Good	15	Good
16. M. P.	29	Aortic insufficiency	Excellent	Normal	3	38.0 (100.4 F.)	40	Good	Good	13	Excellent
17. V. D.	47	Aortic and mitral stenosis and insufficiency; auricular fibrillation	Poor	Large	1	38.1 (100.5 F.)	9	Fair	Good	13	Poor
18. M. D.	32	Aortic insufficiency	Good	Large	3	36.9 (98.4 F.)	3	Good	Good	11	Good
19. N. O.	47	Congenital septal defect	Excellent	Slightly large	7	38.7 (101.6 F.)	110	Good	Good	10	Excellent
20. J. H.	25	Aortic insufficiency	Good	Slightly large	½	37.8 (100 F.)	Few	Good	Good	10	Good
21. H. W.	27	Aortic insufficiency; paroxysmal auricular fibrillation	Excellent	Slightly large	1	38.5 (101.3 F.)	1	Good	Good	11	Good
22. E. J.	54	Aortic insufficiency	Good	Slightly large	2	38.4 (101.1 F.)	Few	Good	Poor	5	Poor
23. L. P.	69	Aortic insufficiency	Excellent	Slightly large	7	37.2 (98.9 F.)	Few	Good	Good	2	Dead *
24. F. S.	69	Aortic stenosis	Good	Slightly large	7	37.9 (102 F.)	40	Good	Good	3	Fair
25. J. K.	39	Uncertain mitral disorder	Excellent	Normal	14	38.1 (100.5 F.)	12	Good	Good	3	Excellent

* Died of progressive cardiac failure.
† Died of unrelated condition.
‡ Died of sudden cardiac accident during therapy.

have carefully compared our 25 patients to see what was the common denominator in the group whose hearts stood the infection well. It soon became obvious that there was no simple solution but that the sum total of a number of factors was responsible for the result.

The factors considered (table 3) were (1) the patient's age, (2) the type of antecedent lesion of the heart, (3) the cardiac reserve before treatment, (4) the size and shape of the heart, as shown by roentgenologic examination, (5) the length of time elapsing between onset of symptoms and start of adequate therapy, (6) the height of the temperature, (7) the intensity of bacteremia, (8) the general clinical appearance, (9) the extent of scarring of the valves as vegetations healed and (10) the care of the heart after therapy.

The factors which bear on cardiac reserve after penicillin therapy may be divided into (1) those operative before inception of treatment (the first eight) and (2) those to be considered afterward (the last

TABLE 4.—*Effect of Age on Cardiac Reserve After Therapy*

| | No Cardiac Failure | | Definite Cardiac Failure | | | |
| | | | Alive | | Dead | |
Age Group, Yr.	No.	%	No.	%	No.	%
Under 30..	8	80	..	....	2	20
30 to 50..	4	57.1	1	14.3	2	28.6
Over 50..	4	50	2	25	2	25

two). Concerning the latter, it might be mentioned that there is no accurate measurement of the amount of scarring caused by absorption of valvular vegetations. It would seem, however, that the degree of distortion would be conditioned by the size and location of the vegetations, which in turn would depend on the situation before treatment was started.

1. *The Age of the Patient.*—A survey of the whole group suggests that youth favors a good result. Eighty per cent of those under 30 years escaped without definite cardiac failure, whereas only 50 per cent of those over 50 years were thus fortunate (table 4). Given 2 persons with apparently similar lesions of the valves, a young man seems to do better than an older man. On the other hand, the oldest patients as a whole had somewhat less extensive lesions of the valves than the youngest, probably because the patients with the worst cardiac conditions of their generation had already died.

2. *The Type of Lesion of the Heart* (table 5).—If the underlying cardiac disease is congenital there seems to be a better prognosis than if it is rheumatic, although the number of cases of congenital disease in this series is too small to be significant. Furthermore, if there are

indisputable signs of mitral stenosis or aortic insufficiency, the prognosis does not seem so good as when the type of cardiac disease or the nature of the lesion of the valve is uncertain. In this "uncertain" group, for instance, are those with lesions of questionable nature of the mitral valve, i. e., those with apical systolic murmurs but no definite diastolic murmur or other clearcut evidence of mitral stenosis. The presence of a serious arrhythmia (notably auricular fibrillation) seems to make the prog-

TABLE 5.—*Effect of the Type of Lesion of the Heart on Cardiac Reserve After Therapy*

| Type of Lesion | No Cardiac Failure | | Definite Cardiac Failure | | | |
| | | | Alive | | Dead | |
	No.	%	No.	%	No.	%
Congenital heart disease......................	2	100				
Uncertain type of lesion......................	5	100				
Definite aortic insufficiency or mitral stenosis....	8	53.3	2	13.3	5	83.3
Definite lesion of valve and serious arrhythmia..	1	33.3	1	33.3	1	33.3

nosis less favorable. It must be remembered that since these patients have previously damaged muscles and valves of the heart they might be expected eventually to show cardiac insufficiency independent of any effect of the bacterial endocarditis.

3. *Cardiac Reserve Before Therapy.*—There is, as would be expected, a high correlation between cardiac reserve before and after therapy (table 6). A few of the patients had long had cardiac symptoms and,

TABLE 6.—*Effect of Previous Cardiac Reserve on Cardiac Reserve After Therapy*

| Previous Cardiac Reserve | No Cardiac Failure | | Definite Cardiac Failure | | | |
| | | | Alive | | Dead | |
	No.	%	No.	%	No.	%
Excellent......................	9	90	..	....	1	10
Good......................	7	87.5	1	12.5		
Fair......................	..	....	1	25	3	75
Poor......................	..	....	1	33.3	2	66.6

of course, did not improve after treatment. Others insisted that they felt better since treatment than they did before because they had learned to take better care of themselves. Some had apparently good reserve before contracting the infection but were already on the verge of failure before administration of penicillin was begun.

In the evaluation of cardiac reserve a rating adapted for our purpose from that of the American Heart Association was used: (1) excellent (no symptoms of cardiac insufficiency on unrestricted activity); (2) good (no symptoms of cardiac insufficiency on slightly restricted activity); (3) fair (mild symptoms of cardiac insufficiency either on mod-

erate activity or under the stress of the infection), and (4) poor (frank symptoms or signs of cardiac failure either before the infection or under its stress).

Of the 18 patients who started out with excellent or good reserve, all but 2 are still in good health; of these, 1 is dead and 1 has definite cardiac failure. On the other hand, of the 7 patients who started treatment with fair or poor reserve, 5 are dead and 2 have definite cardiac failure.

4. *The Size and Shape of the Heart as Shown by Roentgenologic Examination.*—The use of the roentgenogram is another objective method of estimating cardiac reserve before therapy (table 7). Five patients had no cardiac enlargement, and all are now in good health. Thirteen had slight or questionable general cardiac enlargement or prominence of one part of the heart; of these, 6 are doing well, 2 have symptoms

TABLE 7.—*Relationship Between Size of Heart Before Treatment and Cardiac Reserve After Treatment*

Size of Heart as Shown in the Roentgenogram	No Cardiac Failure		Definite Cardiac Failure			
			Alive		Dead	
	No.	%	No.	%	No.	%
Normal..	5	100				
Slightly large *.................................	7	53.8	2	15.4	4	30.8
Large...	4	57.1	1	14.3	2	28.6

* Includes those with slight prominence of one part of the shadow of the heart and with size "at the upper limits of normal."

of cardiac failure and 5 are dead (1 of an unrelated condition). Of the 7 who started out with considerable cardiac enlargement, 4 are doing well, 1 has chronic cardiac failure and 2 are dead. Except for the fact that all in the first group are doing well, there is then no absolute correlation. There is almost no difference between those with only slight abnormality of the cardiac silhouette and those with considerable enlargement. A number did badly who at first had only questionable cardiac hypertrophy, and several are doing well who started out with enlarged hearts. Incidentally, some of the youngest men had the largest hearts, and some of the oldest men had the smallest. This again suggests that the patients with the worst cardiac conditions die before they reach the older age groups.

5. *The Length of Time Between Onset of Symptoms and Beginning of Adequate Therapy.*—There is some correlation between the promptness of treatment and the results, but it is not so high as might be expected (table 8). Obviously, though, in the individual case the risk increases with time. Furthermore, several of the long periods include weeks or months of repressive therapy. Such subcurative therapy is

probably not entirely lost time. Several patients were finally treated successfully after long periods of inadequate but repressive therapy, varying from one month to about twelve months. Besides penicillin, sulfonamide drugs had also been given to some. On the other hand, there were 2 fatalities in cases in which the adequate dose was given only after time had been lost in subcurative treatment. In these cases, this period may have been critical.

TABLE 8.—*Effect on Cardiac Reserve of the Length of Time Between Onset of Symptoms and the Beginning of Adequate Therapy*

| | No Cardiac Failure | | Definite Cardiac Failure | | | |
| | | | Alive | | Dead | |
Length of Time, Mo.	No.	%	No.	%	No.	%
2 or less	7	63.6	3	27.3	1	9.1
2 to 4	4	57.2	..	....	3	42.8
Over 4	5	71.4	..	....	2	28.6

6. *The Height of the Temperature.*—There is obvious significant correlation between extremely high temperature and poor results, all the patients with an average temperature of 39 C. (102.2 F.) or over having died (table 9). However, with the other three groups the correlation is almost negligible. It might be concluded that unless the fever is unusually severe there is a good chance of getting a satisfactory result, other things being equal.

TABLE 9.—*Effect of the Height of Temperature on Cardiac Reserve After Treatment*

| | No Cardiac Failure | | Definite Cardiac Failure | | | |
| | | | Alive | | Dead | |
Average Daily Temperature	No.	%	No.	%	No.	%
Below 38 C. (100.4 F.)	4	66.6	1	16.7	1	16.7
38 to 38.4 C. (100.4 to 101.1 F.)	3	60	2	40		
38.5 to 38.9 C. (101.3 to 102 F.)	9	100				
39 C. (102.2 F.) or over	..	....	..	....	5	100

7. *The Intensity of Bacteremia.*—There would appear to be only little correlation between the number of bacteria and the results. The patient with the highest colony count (400 per cubic centimeter) did not survive, but otherwise there is no particular parallel. There is not even much relationship between the intensity of the bacteremia and the height of the temperature or the clinical appearance. The resistance of the organism to penicillin should be regarded as important mainly when it affects the length of time which elapses before the start of adequate treatment and therefore is not here considered as a factor influencing subsequent cardiac reserve.

8. *The General Clinical Appearance.*—Several patients looked so ill that they obviously constituted poor risks from the start. This appearance was in general a more accurate indication of the outcome than the measurable intensity of the bacteremia. Some patients looked well, and apparently constituted good risks.

Taken together, the temperature, bacterial count and clinical appearance are measures of the severity of the infection and as such would be expected to strongly influence the results.

9. *Increased Distortion of the Valves Under the Influence of Penicillin.*—Several patients showed an apparent acceleration of the destructive process while they were getting penicillin. Admitting that it is hard to separate the results of the disease from those of treatment, it seemed in some cases that the sudden failure of the heart was out of proportion to the conditions present at the start of treatment. L. P. is the leading example. Except for the facts that he was an older man with a definite aortic insufficiency and had had a period of subcurative therapy, there was much in his favor. He felt well, had almost no fever, had few bacteria and had no signs of failure. Nevertheless, just when the lesions should have been healing well there developed sudden alarming cardiac insufficiency, from which he never recovered. It seemed not unlikely that as the vegetations healed his valve was increasingly scarred and distorted.

E. J. had long been followed in the clinic with the diagnosis of aortic stenosis, never having shown the physical signs of aortic insufficiency despite numerous attempts to discover them. However, a few weeks after treatment was started there appeared a faint aortic diastolic blow which subsequently became loud. It is hard to say how much of this structural change was due to the infection and how much to the resolution of the lesion under the influence of penicillin, but it seems that the latter must be considered until more evidence is forthcoming.

10. *Care of the Heart After Treatment.*—Another important factor after therapy is reasonable restriction of activity. This is, of course, an individual matter, inasmuch as what would be reasonable activity in one might be excessive in another. However, this problem is not peculiar to patients cured of subacute bacterial endocarditis; it is a fundamental problem of cardiology in general. At least 2 of our patients, under social and economic pressure, greatly transgressed the limits of reason in this respect despite repeated warnings, and both suffered cardiac failure as a result. On the other hand, most of the patients have taken their infection as a warning and have learned to live within reasonable restrictions, so that they profess to feel better now than before they were stricken with the disease. Only years of observation will tell whether or not their life expectancy will be significantly reduced.

COMMENT

The important factors which seem to determine cardiac efficiency after therapy are the reserve and size of the heart at the time treatment is begun, the patient's age, the type of lesion of the heart, the general clinical appearance and the height of the temperature. In the individual case, some of these factors become more and more unfavorable as adequate treatment is postponed, although, statistically, the time between onset of disease and start of treatment bears less correlation.

As important as these factors are, no one of them can be correlated exactly with the outcome. For instance, L. P. had an extremely low temperature and M. T. a fairly high one; yet there was a good result in the latter and a poor result in the former. Likewise, C. D. had

TABLE 10.—*Values Used in Rating the Liability of Patients to Cardiac Failure After Treatment with Penicillin*

1. Age:			5. Length of time until treatment:	
Below 30	1		Under 2 months	1
30 to 50	2		2 to 4 months	2
Above 50	3		Over 4 months	3
2. Type of lesion of the heart:			6. Height of average temperature:	
Congenital	1		Under 38 C. (100.4 F.)	1
Uncertain	2		38 to 38.4 C. (100.4 to 101.1 F.)	2
Definite mitral stenosis or aortic insufficiency	3		38.5 to 38.9 C. (101.3 to 102 F.)	3
Serious arrhythmia	4		Over 39 C. (102.2 F.)	4
3. Previous cardiac reserve:			7. Bacteria per cc.:	
Excellent	1		Less than 50	1
Good	2		More than 50	2
Fair	3			
Poor	4		8. General clinical appearance:	
			Good	1
			Fair	2
4. Roentgenologic appearance of the heart:			Poor	3
Normal	1			
Slight enlargement	2		9. Care of the heart after treatment:	
Considerable enlargement	3		Good	0
			Poor	2

fever for only one month, and J. K. had fever for fourteen months; yet the former is dead, and the latter is in good health. R. D., a young man, died before treatment was complete, whereas J. D., an old man, does hard physical work without the slightest difficulty two years after therapy. C. B. was an athlete, whereas V. D. had mild cardiac failure and auricular fibrillation for years; yet the former is dead, and the latter manages to get along not much worse than he did before treatment.

It seems, therefore, that the outcome is a composite result of several factors. Although the more one feature is against a patient, the less are his chances, yet if other things are favorable he may survive without appreciable deterioration of cardiac function. It is a combination of unfortunate circumstances, not just one, which makes extirpation of the infection a Pyrrhic victory.

A fairly accurate prognosis can be made by estimation of the combined effect of various factors. For instance, if numerical values are assigned to each of the various factors (table 10), the sum total, or

"liability rating" of a patient, approximates fairly closely the actual status after treatment (table 11). All our patients with a total "liability rating" of more than 19 are dead, whereas all with a rating of less than 16 are alive and in good health (with the exception of L. P.). In the case of L. P. and the intermediate group, it may well have been the unmeasurable increase of valvular distortion under the influence of penicillin which was critical.

Of all the factors discussed, the only one which is really amenable to change by the physician is the length of time between onset of symptoms and the start of adequate therapy. However, several of the most alarming features—high temperature, general clinical appearance and, most important of all, the cardiac reserve at the beginning of therapy—are more or less functions of the length of time consumed while the patient awaits the start of therapy. For instance, when penicillin first

TABLE 11.—*Liability Rating Compared with Present Cardiac Reserve*

Name	Rating	Present Status	Name	Rating	Present Status
C. B.	23	Dead	M. D.	15	Good
V. T.	23	Dead	L. C.	14	Good
E. G.	21	Dead	M. T.	14	Good
C. D.	20	Dead	R. L.	14	Good
R. D.	20	Dead	H. W.	14	Good
V. D.	19	Poor	O. S.	13	Excellent
A. S.	18	Dead	J. D.	13	Excellent
B. S.	18	Fair	S. M.	13	Good
E. J.	17	Poor	J. K.	13	Excellent
F. H.	16	Poor	M. S.	12	Excellent
L. P.	15	Dead	M. P.	12	Excellent
F. S.	15	Fair	J. H.	12	Good
N. C.	15	Good			

became available for treatment of subacute bacterial endocarditis, we used it in several patients, in whom the disease was obviously well advanced. One of these (C. B.) had been an athlete before the onset of infection but had signs of early cardiac failure by the time treatment was started. There is every reason to believe that he would not have suffered subsequent fatal decompensation had we been able to treat him a few months earlier. It is of interest that none of the patients we have treated recently have been nearly so ill. In general they have been treated before the process had gone to this apparently irreversible stage, and the incidence of cardiac failure has seemed to decrease.

If this wasted time is to be reduced to a minimum, two imperative demands confront the physician: (1) early diagnosis of the nature of the disease and (2) determination of the organism's degree of resistance to penicillin. Both are obviously necessary; the first is in itself not enough. Failures will continue to occur if subacute bacterial endocarditis is unsuspected or if precious time is lost in giving subcurative doses of penicillin.

SUMMARY AND CONCLUSIONS

1. Cardiac failure is important, or potentially so, in a large majority of untreated patients with subacute bacterial endocarditis. Eighty per cent of our series of 40 untreated patients followed to autopsy had evidence of cardiac failure of more or less chronicity.

2. Statistically, treatment with penicillin postpones cardiac failure and reduces its incidence. Approximately 30 per cent of our series of 25 treated patients suffered cardiac failure.

3. Cardiac failure after otherwise successful treatment is the result of an interplay of a number of factors, no one of which is exclusively responsible.

4. The most important factors are the previous reserve and size of the heart, the patient's age, the type of lesion of the heart, the height of the temperature, the general clinical appearance and the length of time before adequate treatment.

5. The one factor amenable to change by the physician is the length of time elapsing before the start of adequate therapy. This demands (*a*) early diagnosis of the nature of the disease and (*b*) determination of the degree of the organism's resistance to penicillin.

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MERCURIAL DIURETICS

A Comparison of Acute Cardiac Toxicity in Animals and the Effect of Ascorbic Acid on Detoxification in Their Intravenous Administration

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ACUTE toxicity of mercurial diuretics has been noted frequently, but no extensive investigation of substances to counteract this toxicity has been reported.[1] There are two apparently distinct immediate reactions in human beings—a nonfatal hypersensitivity [2] and a fatal cardiac reaction. Experiments in animals [1a] and observations in human beings [1c] have determined that death is caused by ventricular fibrillation.

Ascorbic acid has been used to detoxify chemotherapeutic heavy metals, especially arsenic.[3] It is an effective physiologic reducing agent. Certain animals, including dogs, can synthesize ascorbic acid and are therefore suitable experimental animals.

We have extended the investigation of the mechanism of immediate death in dogs from mercurial diuretics for the three commonly employed ones, mercurophylline injection, mersalyl and theophylline and mercuhydrin. We have also studied the possible detoxifying effect of ascorbic acid on these preparations.

The addition of another substance to a mercurial diuretic in an effort to prevent fatal reactions should have, according to Pines and his asso-

1. (a) Barker, H. M.; Lindberg, H. A., and Thomas, M. E.: Sudden Death and Mercurial Diuretics, J. A. M. A. 119:1001 (July 25) 1942. (b) DeGraff, A. C., and Nadler, J. E.: A Review of the Toxic Manifestations of Mercurial Diuretics in Man, ibid. 119:1006 (July 25) 1942. (c) Volini, I. E.; Levitt, R. O., and Martin, R.: Sudden Death Following Mercurial Diuresis, ibid. 128:12 (May 5) 1945. (d) Wexler, J., and Ellis, L. B.: Toxic Reactions to the Intravenous Injection of Mercurial Diuretics, Am. Heart J. 27:86 (Jan.) 1944.

2. Wolf, I. J., and Bongiorno, H. D.: Sudden Death with Salyrgan, Canad. M. A. J. 25:73 (July) 1931.

3. Bundesen, H. N.; Aron, H. C. S.; Greenbaum, R. S.; Farmer, C. J., and Abt, A. F.: The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy, J. A. M. A. 117:1692 (Nov. 15) 1941.

ciates,[4] three qualities. It should not decrease the diuretic effect, but, on the other hand, it should increase it. It should be innocuous in the dose recommended and should be miscible without forming a precipitate.

Ascorbic acid in combination with mercurophylline injection has been found by one of us (C. F. S.)[5] to increase the diuretic effect in human beings up to 50 per cent. This substance can be given intravenously in large doses without producing a toxic reaction. It can be mixed with mercurial preparations prior to administration without forming a precipitate.

METHOD

Mercurophylline injection (Campbell Products, Inc.), mersalyl and theophylline (Winthrop Chemical Company, Inc.) and mercuhydrin (Lakeside Laboratories, Inc.) were administered alone and in conjunction with ascorbic acid (Abbott Laboratories). The ascorbic acid was injected before and with the aforementioned preparations at different intervals of time. The dogs used in these experiments were maintained in anesthesia with a 2.5 per cent solution of pentobarbital sodium and were connected with an artificial respirator.

In the control dogs, mercurophylline injection, mersalyl and theophylline and mercuhydrin were administered in doses of 1 cc. into the femoral vein at two and five minute intervals. Ascorbic acid was administered in doses of 150 mg. ten minutes prior to the injection of 1 cc. of mercuhydrin at two minute intervals, and 250 mg. was mixed with 1 cc. of each of the mercurial preparations and given simultaneously at two and five minute intervals. Electrocardiographic records were obtained before and during the injection. Lead II was used to demonstrate the conduction disturbances. The lethal dose of a mercurial preparation was considered to be the development of bradycardia of less than 30 beats per minute or a ventricular asystole or a ventricular fibrillation.

RESULTS

A comparison of the lethal doses for mercurophylline injection, mersalyl and theophylline and mercuhydrin is shown in table 1. It can be noted that mercuhydrin was the least toxic of the three mercurial preparations employed, whereas mercurophylline injection and mersalyl and theophylline were about equal in toxicity.

It is to be noted in table 2 that the lethal doses of mercurophylline injection and of mersalyl and theophylline were not altered by the administration of ascorbic acid. The lethal dose of mercuhydrin, on the other hand, was definitely increased when ascorbic acid was administered either prior to or simultaneously with mercuhydrin.

The mechanism of the death from cardiac toxicity produced by mercurophylline injection and by mersalyl and theophylline either alone

4. Pines, I.; Sanabria, A., and Hernandez Arriens, R. T.: Mercurial Diuretics: The Addition of Magnesium Sulfate to Prevent the Toxic Effects of Their Intravenous Administration, Brit. Heart J. **6**:197 (Oct.) 1944.

5. Shaffer, C. F.: The Diuretic Effect of Ascorbic Acid: Preliminary Report on Its Use in Cardiac Decompensation, J. A. M. A. **124**:700 (March 11) 1944.

or with ascorbic acid is due to ventricular fibrillation, as noted in figures 1 and 2. Death following administration of mercuhydrin alone or in combination with ascorbic acid is due to ventricular asystole, as noted in figure 3.

COMMENT

Fatalities in human beings occur suddenly after the administration of a mercurial diuretic. Death has been attributed to ventricular fibril-

TABLE 1.—*The Lethal Doses for Mercurophylline Injection, Mersalyl and Theophylline and Mercuhydrin Administered Intravenously to Dogs*

Drug	No. of Dogs	Average Weight, Kg.	Amount Given at 2 and 5 Min. Intervals, Cc.	Average Total Given at 2 Min. Intervals (6 Dogs), Cc.	Average Total Given at 5 Min. Intervals (5 Dogs), Cc.	Minimum Lethal Dose/Kg. at 2 Min. Intervals, Cc.	Minimum Lethal Dose/Kg. at 5 Min. Intervals, Cc.
Mercurophylline injection.......	11	6.1	1.0	2.0	1.2	0.29	0.14
Mersalyl and theophylline...	11	6.4	1.0	2.2	3.0	0.52	0.52
Mercuhydrin.....	11	7.3	1.0	8.3	11.0	1.14	1.52

TABLE 2.—*The Lethal Doses for Mercurophylline Injection, Mersalyl and Theophylline and Mercuhydrin Combined with Ascorbic Acid and Administered Intravenously to Dogs*

Drug	No. of Dogs	Average Weight, Kg.	Amount of Mercurials Given at 2 and 5 Min. Intervals, Cc.	Amount of Ascorbic Acid Given/ Cc. of Mercurials, Mg.	Amount of Ascorbic Acid Given Prior to Mercuhydrin, Mg.	Average Total Given at 2 Min. Intervals, Cc.	Average Total Given at 5 Min. Intervals (5 Dogs), Cc.	Minimum Lethal Dose/ Kg. at 2 Min. Intervals, Cc.	Minimum Lethal Dose/ Kg. at 5 Min. Intervals, Cc.
Mercurophylline injection.......	10	5.2	1.0	250	...	1.0 (5 dogs)	1.4	0.18	0.31
Mersalyl and theophylline...	10	7.6	1.0	250	...	3.2 (5 dogs)	3.0	0.41	0.40
Mercuhydrin.....	17	6.8	1.0	250	150	11.4 (7 dogs) 12.8 (5 dogs)*	16.8	1.74 1.69*	2.47

* Given ascorbic acid ten minutes prior to mercuhydrin.

lation.[1c] Any substance, therefore, that prevents death following administration of a mercurial diuretic should have an immediate detoxifying effect. Ascorbic acid, according to our studies, reduces the toxicity of mercuhydrin.

The mechanism of death from cardiac toxicity produced by mercurials in animals has been demonstrated to be relatively constant and independent of anesthesia, sectioning of nerves and perfusion of an isolated heart.[1a]

DeGraff and Lehman,[6] in a report on the acute toxicity of the mercurial diuretics, stated that the lethal dose of a mercurial diuretic in animals is inversely proportional to the rate of injection. This has been explained by Modell,[7] in that certain substances develop their actions slowly, and consequently, when injected rapidly, the true minimal lethal dose may be exceeded.

The average mean lethal dose for mercuhydrin when given at two minute intervals was definitely less than that with five minute intervals. The average mean lethal dose for mercurophylline injection or mersalyl
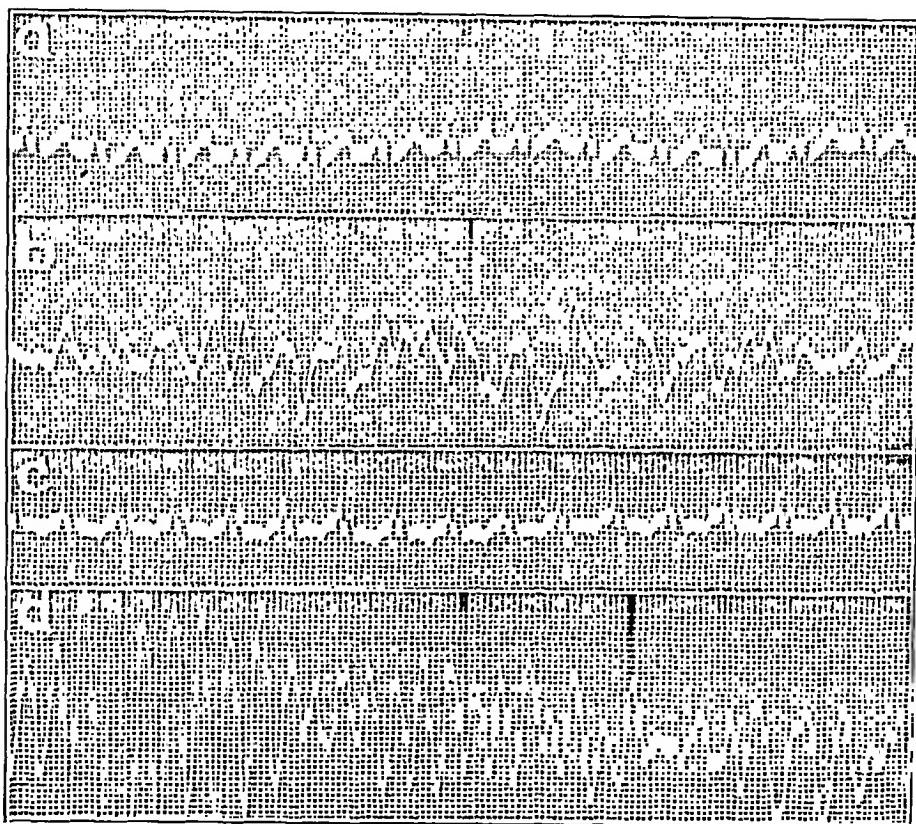
Fig. 1.—(*a*), lead II of a control prior to intravenous administration of mercurophylline injection. (*b*), ventricular fibrillation after injection of 1 cc. (*c*), lead II of a control prior to intravenous injection of mercurophylline and ascorbic acid. (*d*), ventricular tachycardia proceeding to ventricular fibrillation after injection of 2.25 cc. (1 cc. of mercurophylline injection and 1.25 cc. of ascorbic acid).

and theophylline when given at five minute intervals was not significantly different, however, from that at two minute intervals. This may be explainable on the basis of the mechanism of cardiac failure produced

6. DeGraff, A. C., and Lehman, R. A.: The Acute Toxicity of Mercurial Diuretics, J. A. M. A. **119**:998 (July 25) 1942.

7. Modell, W., and Krop, S.: Acute Toxicity of Mercurial Diuretics, Proc. Soc. Exper. Biol. & Med. **55**:80 (Jan.) 1944.

by mercuhydrin as compared with that produced by the other two mercurial preparations.

All the dogs receiving mercurophylline injection alone or in combination with ascorbic acid died in ventricular fibrillation. All but 1 of the dogs given mersalyl and theophylline either alone or with ascorbic acid also died in ventricular fibrillation. The 1 animal in which ventricular asystole developed tolerated more than twice the amount of this preparation than the average of the others receiving mersalyl and
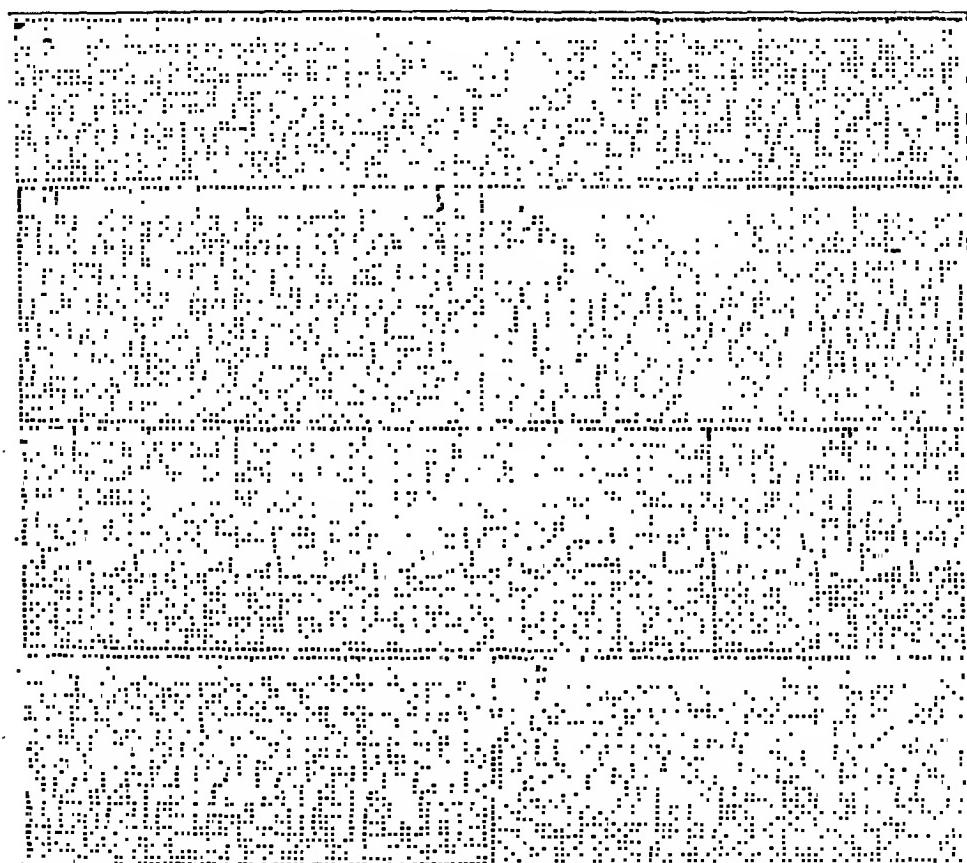
Fig. 2.—(*a*), lead II of a control prior to intravenous administration of mersalyl and theophylline. (*b*), ventricular tachycardia after injection of 1 cc. (*c*), ventricular fibrillation after injection of 2 cc. (*d*), lead II of a control prior to intravenous administration of mersalyl and theophylline and ascorbic acid. (*e*), altered ventricular complexes after injection of 4.5 cc. (2 cc. of mersalyl and theophylline and 2.5 cc. of ascorbic acid). (*f*), ventricular fibrillation after injection of 6.75 cc. (3 cc. of mersalyl and theophylline and 3.75 cc. of ascorbic acid).

theophylline. In contrast, all but 1 dog when given mercuhydrin, either alone or with ascorbic acid, died of ventricular asystole. The 1 animal in which ventricular fibrillation developed received the smallest amount of mercuhydrin.

Bundesen and his associates[3] reported the detoxifying effect of ascorbic acid on arsenical compounds in human beings and concluded that the addition of this substance, by its reducing effect, inhibited the
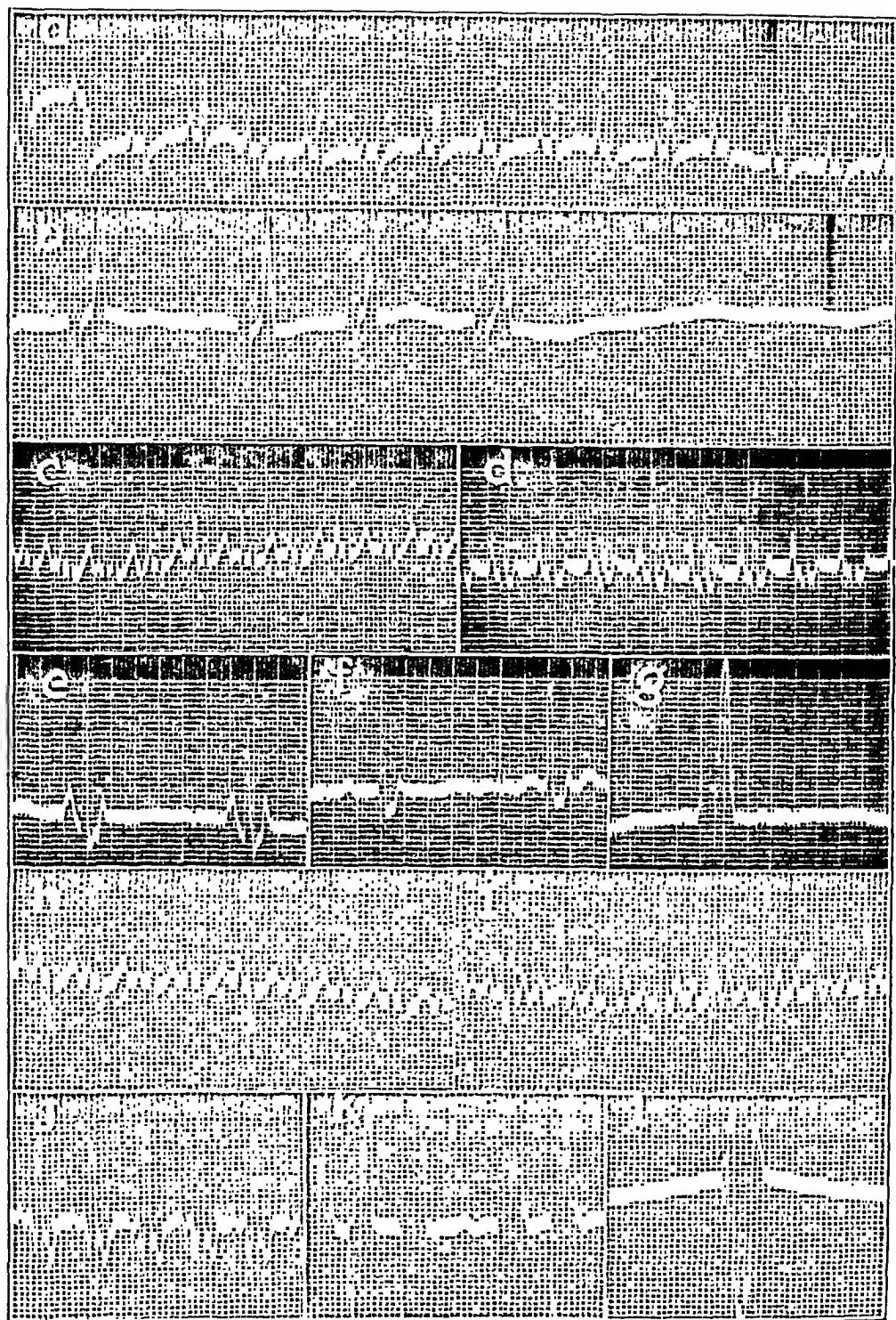
Figure 3
(See legend on opposite page)

oxidation of the arsenic radical. McChesney and others [8] investigated the effect of ascorbic acid on arsenicals in animals and also stated the belief that the detoxifying action was by this method. Marin [9] reported effective results in ascorbic acid therapy of nonfatal hypersensitivity reactions to mercury in human beings and found that ascorbic acid in vitro reduced the mercuric salt to mercurous salt and then to the inert metal.[10]

Ascorbic acid was given prior to and simultaneously with the administration of mercuhydrin, and the results were compared. A dose of 150 mg. of ascorbic acid given ten minutes before the injection of 1 cc. of this mercurial preparation had less detoxifying effect than when given simultaneously. McChesney and his associates [8] noted in animals that ascorbic acid gave the greatest protection when these substances were administered together. We, therefore, combined ascorbic acid with the mercurial preparations and administered them simultaneously in the remainder of the experiments.

8. McChesney, E. W.; Barlow, O. W., and Klinck, G. H., Jr.: The Detoxication of Neoarsphenamine by Means of Various Organic Acids, J. Pharmacol. & Exper. Therap. **80**:81 (Jan.) 1944.

9. Marin, J. V.: Ascorbic Acid Therapy of Mercurial Stomatitis Caused by Antisyphilitic Therapy with Report of Cases, Rev. méd. de Rosario **31**:1127 (Nov.) 1941.

10. Marin, J. V.: Ascorbic Acid Therapy of Acute Mercurial Intoxication in Guinea Pigs, Rev. Soc. argent. de biol. **17**:581 (Nov.) 1941.

EXPLANATION OF FIGURE 3

Fig. 3.—(*a*), lead II of a control at a rate of 150 per minute prior to intravenous administration of mercuhydrin at five minute intervals in a 7 Kg. dog. (*b*), relative bradycardia at a rate of 75 per minute, with idioventricular rhythm after injection of 10 cc. before ventricular asystole. (*c*), lead II of a control at a rate of 150 per minute prior to intravenous administration of mercuhydrin and ascorbic acid at two minute intervals in a 6.5 Kg. dog. (*d*), slightly altered ventricular complexes with incipient depression of the ST segment after injection of 18 cc. (8 cc. of mercuhydrin and 10 cc. of ascorbic acid), the calculated minimum lethal dose of mercuhydrin for the dog at this interval of injection. (*e*), relative bradycardia at a rate of 36 per minute with altered ventricular complexes and depression of the ST segment after injection of 27 cc. (12 cc. of mercuhydrin and 15 cc. of ascorbic acid), 50 per cent more than the minimum lethal dose. (*f*), similar recording after injection of 31.50 cc. (14 cc. of mercuhydrin and 17.50 cc. of ascorbic acid), 75 per cent more than the minimum lethal dose. (*g*), idioventricular rhythm and complexes before ventricular asystole after injection of 36 cc. (16 cc. of mercuhydrin and 20 cc. of ascorbic acid), 100 per cent more than the minimum lethal dose. (*h*), lead II of a control prior to intravenous administration of mercuhydrin and ascorbic acid at five minute intervals in a 6.5 Kg. dog. (*i*), similar record after injection of 22.50 cc. (10 cc. of mercuhydrin and 12.50 cc. of ascorbic acid), the calculated minimum lethal dose for the dog at this interval of injection. (*j*), altered ventricular complexes with depression of the ST segment after injection of 33.75 cc. (15 cc. of mercuhydrin and 18.75 cc. of ascorbic acid), 50 per cent more than the minimum lethal dose. (*k*), idioventricular rhythm and complexes after injection of 45 cc. (20 cc. of mercuhydrin and 25 cc. of ascorbic acid), 100 per cent more than the minimum lethal dose. (*l*), ventricular complexes immediately before ventricular asystole.

Doses of 250 mg. of ascorbic acid and 1 cc. of mercuhydrin given at two minute intervals increased the average minimal lethal dose of this mercurial preparation by more than 50 per cent. Ascorbic acid and mercuhydrin given at five minute intervals increased the average minimal lethal dose by 66 per cent. It is possible that, with longer intervals of time, use of ascorbic acid may have progressively increased this average. Pines and his associates [4] used intervals of thirty minutes in their investigation of the detoxifying effect of another substance, magnesium sulfate.

The results of our experiments suggest that the greatest cardiac toleration for a mercurial diuretic occurs with mercuhydrin, which is the least likely to induce ventricular fibrillation, and that the detoxifying value of ascorbic acid is greatest for this preparation.

A method of predicting a fatal reaction in human beings is not available. Nonfatal hypersensitivity reactions, tachycardia or premature ventricular systoles may occur after intravenous administration.[2] Because such manifestations may be premonitory signs of a fatal reaction, it is thought that mercuhydrin combined with ascorbic acid is the diuretic preferred in such cases.

Mercuhydrin had the least cardiac toxicity of the three mercurials employed, and the addition of ascorbic acid increased its lethal dose. We, therefore, investigated the diuretic effect of this combination in human beings. Modell [11] has previously found that mercuhydrin is as effective a diuretic as mercurophylline injection and that the optimum dose is 2 cc. Twenty patients with cardiac failure have been studied to date. Mercuhydrin in doses of 2 cc. has been mixed with 500 mg. of ascorbic acid (Abbott Laboratories) and administered intravenously, with a result equal to or an actual increase of the diuretic effect up to 50 per cent. This clinical investigation is being continued and will be reported later in detail.

SUMMARY

Mercuhydrin was the least toxic of the three mercurial diuretics studied. The administration of ascorbic acid prior to or simultaneously with mercuhydrin definitely reduced the toxicity of this preparation, but when given with mercurophylline injection and with mersalyl and theophylline it had no detoxifying effect.

The usual mechanism of death produced by mercuhydrin, with and without ascorbic acid, was ventricular asystole and by mercurophylline injection and mersalyl and theophylline was ventricular fibrillation.

Twenty patients in cardiac failure who have received mercuhydrin with ascorbic acid intravenously to date have had an equal or an increased diuresis up to 50 per cent.

11. Modell, W.; Gold, H., and Clarke, D. A.: Quantitative Observations on Mercuhydrin and Mercupurin, J. Pharmacol. & Exper. Therap. **84**:284 (July) 1945.

EXPERIMENTALLY INDUCED INFECTIOUS HEPATITIS

Roentgenographic and Gastroscopic Observations

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THE OCCURRENCE of anorexia, nausea, vomiting and abdominal pain during the preicteric and early icteric phases of infectious hepatitis has suggested that involvement of the gastrointestinal tract may be an important feature of this disease. The fact that the etiologic agent of infectious hepatitis is eliminated in the stools of patients in the acute phase of the disease and may be transmitted experimentally by feeding such material to human volunteers adds supporting evidence to this concept.[1] More objective criteria have been afforded by the demonstration at autopsy of regional lymphadenopathy as well as edema and phlegmonous changes in the stomach and small and large bowel in fatal cases.[2]

In an effort to demonstrate changes in the gastrointestinal tract during infectious hepatitis, certain roentgenologic and gastroscopic

1. (*a*) MacCallum, F. O., and Bradley, W. H.: Transmission of Infective Hepatitis to Human Volunteers, Correspondence, Lancet 2:228 (Aug. 12) 1944. (*b*) Havens, W. P., Jr.; Ward, R.; Drill, V. A., and Paul, J. R.: Experimental Production of Hepatitis by Feeding Icterogenic Materials, Proc. Soc. Exper. Biol. & Med. 57:206-208 (Nov.) 1944. (*c*) Neefe, J. R.; Stokes, J., Jr., and Rheinhold, J. G.: Oral Administration to Volunteers of Feces from Patients with Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis, Am. J. M. Sc. 210:29-32 (July) 1945.

2. Pathology of Infective Hepatitis, editorial, Brit. M. J. 1:17-18 (Jan. 6) 1945. Gowen, G. H.: The Epidemiology of Epidemic Hepatitis, Bull. U. S. Army M. Dept., January 1945, no. 84, pp. 41-50. Havens, W. P., Jr.: Unpublished data.

studies have been made. Pöschl [3] has reported alteration in the antral portion of the stomach and first part of the ·duodenum, interpreted as evidence of gastroduodenitis. The ·patients in whom these changes. were found were far along in the course of their disease; 50 per cent of them had only scleral icterus left, and the other half were no longer jaundiced. More recently, Knight and Cogswell [4] reported gastroscopic observations, with changes generally interpreted as superficial gastritis in 7 out of 9 patients during the preicteric and early icteric phases of naturally occurring infectious hepatitis. The antral portion of the stomach was primarily involved and in some instances the fundus. Five of these patients had small aphthous ulcers, from 2 to 5 mm. in diameter, in the antrum and on the angularis. In contrast are the essentially normal observations of Bank and Dixon.[5] It is to be noted, however, that most of their patients had gastroscopy performed at least three weeks after the onset of hepatitis.

During the past eight months, experiments in the transmission of infectious hepatitis to human volunteers conducted by the Neurotropic Virus Disease Commission have offered an opportunity to study the appearance of the gastrointestinal tract at various times during the course of disease by roentgenogram and the gastroscope. It is the object of this paper to describe these observations.

MATERIALS AND METHODS

Subjects.—Twenty-one healthy male human volunteers ranging in age from 19 to 27 years were employed as experimental subjects. They were divided into two groups. Group I was composed of 9 subjects who had roentgenographic examination made of the stomach and duodenum at some time during the acute phase of their infectious hepatitis. Group II was composed of 12 men who had roentgenographic examination of the upper part of the gastrointestinal tract before experimental inoculation and again during the acute and convalescent phases of disease. Six of these men also had gastroscopic examinations before experimental inoculation and during the acute and convalescent phases of infectious hepatitis.

Virus.—The strain of infectious hepatitis virus used in this laboratory was originally obtained from the stool of a United States Army soldier (B. E.) who contracted epidemic infectious hepatitis in·Sicily in 1943.[1b] It has been through four passages in human volunteers to date. This agent is filtrable through a Chamberland no. 2 filter and withstands heating to 56 C. (132.8 F.) for at least

3. Pöschl, M.: Röntgenuntersuchungen des Magen-Darmkanals bei Icterus infectiosus, ·Röntgenpraxis **14**:401-405 (Nov.) 1942.

4. Knight, W. A., and Cogswell, R. C.: Preliminary Observations of the Gastric Mucosa in Patients with Infectious Hepatitis, J. A. M. A. **128**:803 (July 14) 1945.

5. Bank, J., and Dixon, C. H.: Gastroscopy in Acute and Chronic Hepatitis, J. A. M. A. **131**:107 (May 11) 1946.

thirty minutes.[6] It has produced the disease in 27 out of 40 human volunteers (including this experiment) inoculated parenterally or orally, with periods of incubation ranging from fifteen to thirty-four days.

Infectious materials employed in this experiment were specimens of serum or stools obtained during the acute phase of disease experimentally induced in human volunteers. Infectious serum was fed or inoculated parenterally, and stool was fed.

Observation of Experimental Subjects.—All subjects were followed for periods of one hundred and ten to one hundred and fifteen days after inoculation. They were instructed to report at once the occurrence of any symptoms, which were then investigated. The volunteers who contracted infectious hepatitis were hospitalized in the Isolation Pavilion of the New Haven Hospital, under our supervision.

Laboratory Observations.—The following tests of hepatic function were performed at weekly intervals on all volunteers who received the material to be tested throughout the two periods of the experiment (four months each; the volunteers who reported symptoms or sickened had more frequent determinations made): (1) quantitative determination of total serum bilirubin content,[7] (2) cephalin-cholesterol flocculation test (Hanger),[8] (3) sulfobromophthalein dye retention test,[9] (4) thymol turbidity test,[10] (5) determination of urobilinogen [11] and determination of bilirubin content [12] in urine. Normal values for each volunteer were established before inoculation. Only volunteers who had symptoms and signs of infectious hepatitis in conjunction with consistently abnormal results in sulfobromophthalein dye retention tests and cephalin-cholesterol flocculation tests were regarded as showing positive evidence of infectious hepatitis. In this study all such patients had clinical jaundice.

RESULTS

When roentgenographic examinations were made on volunteers with experimentally induced infectious hepatitis, certain changes in

6. Havens, W. P., Jr.: Properties of the Etiologic Agent of Infectious Hepatitis, Proc. Soc. Exper. Biol. & Med. **58**:203-204 (March) 1945.

7. The quantitative total serum bilirubin determination was done according to the Method of Malloy and Evelyn (Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481-490 [July] 1937), the photoelectric colorimeter being used.

8. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Investigation **18**:261-269 (May) 1939.

9. A 10 per cent retention in the blood thirty minutes after the intravenous injection of 5 mg. of bromosulfophthalein per kilogram of body weight was considered the maximum normal level (Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112-1114 [April 11] 1925).

10. Maclagan, N. F.: Thymol Turbidity Test: New Indicator of Liver Dysfunction; Preliminary Report, Nature, London **154**:670-671 (Nov. 25) 1944.

11. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698-725 (June) 1925.

12. Sparkman, R.: Studies of Urobilinogen: I. A Simple and Rapid Method for Quantitative Determination of Urobilinogen in Stool and in Urine, Arch. Int. Med. **63**:858-866 (May) 1939.

the duodenum were evident in some of them. These changes were: nonhomogeneous filling of the first portion and proximal part of the second portion of the duodenum, with an increase in the size of the mucosal folds and a corresponding narrowing of the troughs between the folds. There was fluoroscopic evidence of increased irritability of these segments. Filling by the opaque meal resulted in incomplete distention of the lumen and rapid emptying in some cases. In some patients who were severely sick, the prepyloric part of the stomach showed unbalanced peristalsis, coarse mucosal folds and accentuated transverse folds, as seen in cases of antral gastritis.

Group I.—Seven of the 9 volunteers in group I were examined roentgenographically during the preicteric or early icteric period of the

TABLE 1.—*Roentgenologic Findings in Nine Patients with Experimentally Induced Infectious Hepatitis*

	Roentgenogram		
Name	Stomach and Duodenum	Day of Jaundice	Abdominal Symptoms †
G. R.	Normal	1 20	+ 0
H. D.	Normal	2	+++
I. N.	Normal	1 22	++ 0
M. S.	Normal	2 19	+ 0
M. N.	Normal	21	0
H. S.	Normal	2 21	+ 0
F. W.	Duodenitis	—5*	+
S. R.	Duodenitis	8	+
J. S.	Gastroduodenitis	22	0

* Before jaundice.
† Degree of severity is indicated as follows: +, anorexia; ++, anorexia and nausea, and +++, anorexia, nausea and vomiting.

disease, and the remaining 2 were examined after three weeks of jaundice (table 1). The stomach and duodenum of all these patients were normal with the exception of 3 who showed changes compatible with antral gastritis or duodenitis. One man (J. S.) had incomplete filling of the prepyloric part of the stomach, with evidence of enlargement of the mucosal folds. The other 2 patients (F. W. and S. R.) had irregularity, with nonhomogeneous filling of the duodenal cap and increase in longitudinal folds. Coarsening and roughening of the folds of the second portion of the duodenum, with failure of this part to distend, were also evident. Since no preinoculation roentgenographic examinations were made on these 3 men, it is impossible to evaluate the significance of these findings. Moreover, such observations are similar to those made in a number of routine examinations done in cooperation

with Selective Service three years ago by the Department of Radiology, Yale University School of Medicine. At that time, changes were seen in a certain percentage of healthy asymptomatic selectees, similar to those shown in the stomach or duodenum of these 3 patients. Because of these atypical findings in the aforementioned selectees, it cannot be said that the changes in these 3 patients with experimentally induced infectious hepatitis are significant in the absence of control examinations before illness.

Group II.—Because of the difficulty in interpreting the findings when preinoculation roentgenographic examinations were not made, the

TABLE 2.—*Roentgenologic and Gastroscopic Findings in Patients with Experimentally Induced Infectious Hepatitis*

| | | | Acute Phase | | | | | | Convalescent Phase: Gastroscopy, Stomach |
| | | | Roentgenogram | | | Gastroscopy | | | |
Volunteer	Period of Incubation, Days	Severity of Disease	Stomach and Duodenum	Day of Jaundice	Abdominal Symptoms	Stomach	Day of Jaundice	Abdominal Symptoms	
B. T.	23	+	Normal	4	+	Normal	3†	++	Normal
B. K.	26	+++	Normal	1†	++				
C. K.	26	++++	Gastro-duodenitis	6	+	Normal	3	++	Normal
K. Y.	26	++++	Normal	11	0				
S. D.	24	++	Normal	5	0	Superficial gastritis	2†	+++	Normal
K. L.	30	+++	Normal	12	+				
B. S.	27	++	Normal	3	+++	Normal	6†	0	Normal
S. N.	21	++	Normal	2†	+				
V. W.	25	++++	Duodenitis*	7	+	Superficial gastritis	4	++	Superficial gastritis
I. G.	16	++	Duodenitis	1†	++				
T. R.	28	+	Gastro-duodenitis	1	+	Superficial gastritis	7	0	Normal
W. E.	17	+	Duodenitis	2†	++				

* This patient (V. W.) also had roentgenologic evidence of duodenitis before experimental inoculation. Gastroscopic examination revealed normality at that time.
† Before jaundice.

12 subjects of group II had such examination made before experimental inoculation and during the acute phase of disease (table 2). A few of these patients were also examined again during convalescence. All were essentially normal before inoculation, except 1 man (V. W.) who had changes suggestive of duodenitis. When these 12 men were reexamined in the preicteric or early icteric period of their experimentally induced infectious hepatitis, the subject who had previously showed evidence of duodenitis had similar evidence at the second examination. Of the other 11 men, 7 were normal and in 4 there had developed changes in the duodenum compatible with a diagnosis of duodenitis.

Six men in this group also had gastroscopic examinations performed by one of us (S. D. K.), before experimental infection, during the acute phase of disease and again during convalescence. All 6 had normal-appearing gastric mucosa before experimental infection. During the acute preicteric or early icteric phase of disease, changes in the gastric mucosa compatible with a diagnosis of acute superficial gastritis developed in 3 of these men. The mucosa was fiery red and edematous, with small pools of grayish exudate between the folds. No ulcers were visible. In 2 of the men these changes had receded perceptibly in convalescence, while the third man still had residual change present seven weeks after onset of disease.

In this article are recorded the histories of the cases of 2 of the patients in whom evidence of gastritis and/or duodenitis developed during the acute phase of experimentally induced infectious hepatitis. Preinoculation studies of these patients had shown them to be normal.

REPORT OF CASES

CASE 1.—S. D., a 26 year old healthy white man, contracted infectious hepatitis on Aug. 12, 1945, twenty-four days after ingesting 0.5 cc. of infectious serum. The onset was gradual, with intermittent cramplike abdominal pain and listlessness. Fever developed with a temperature of 103.6 F. (rectally) on the sixth day of disease, and clinical jaundice appeared on the twelfth day, persisting for eight days. The maximum measured height of total serum bilirubin was 1.4 mg. per hundred cubic centimeters. The course of the disease was mild, and recovery was complete. Preinoculation roentgenographic and gastroscopic examinations of the stomach and duodenum had revealed them to be normal. Gastroscopic examination on the tenth day of disease (August 21), when nausea and vomiting were present, revealed a normal antrum but a fiery red edematous mucosa in the body of the stomach. Small pools of grayish exudate were seen between the edematous folds of the mucosa. One week later, when the abdominal symptoms were ameliorated (August 27), roentgenographic examination of the stomach and duodenum showed normality. Eight weeks after onset, during convalescence, when the patient was asymptomatic, gastroscopic examination revealed a normal mucosa.

CASE 2.—C. K., a 20 year old healthy white man, contracted infectious hepatitis (Aug. 14, 1945) twenty-six days after ingesting 0.5 cc. of infectious serum. The onset was acute, with anorexia, a temperature of 101 F. (rectally) and generalized fatigue. Clinical jaundice appeared on the sixth day of disease and persisted for twenty-seven days. The maximum measured height of serum bilirubin was 23.0 mg. per hundred cubic centimeters. The course of disease was severe, but recovery was complete. Preinoculation roentgenographic and gastroscopic examinations of the stomach and duodenum had revealed them to be normal. During the first week of jaundice, when the patient had anorexia and nausea, these examinations were repeated. The roentgenogram (August 24) revealed roughening and failure of homogeneous filling of the prepyloric part of the stomach. The duodenal bulb was ragged, without homogeneous filling, and there was an increase in the longitudinal folds. The proximal portion of the second part of the duo-

denum was tubular, without proper distention, while the distal second portion of the duodenum showed considerable increase in mucosal folds. Gastroscopy at this time (August 21) revealed normal gastric mucosa. During convalescence, when the patient was asymptomatic, seven weeks after onset of disease, gastroscopy was performed again, revealing a normal gastric mucosa.

COMMENT

In this paper, attention has been called to previous observations of others [13] on the occurrence of roentgenologic and gastroscopic changes in the stomach and duodenum of patients with epidemic infectious hepatitis. Similar examinations made in this laboratory on patients with experimentally induced infectious hepatitis have confirmed these findings. However, it has been pointed out that the appearance of changes supposedly characteristic roentgenologically of gastritis and/or duodenitis in patients with experimentally induced infectious hepatitis is of little significance unless previous control preinoculation studies have been made, since similar changes have been observed in a certain percentage of asymptomatic young men during examination for Selective Service. When preinoculation roentgenographic examinations were made in 12 healthy human volunteers, 1 was found to have changes suggestive of duodenitis. The fact that in 4 of the remaining 11 normal subjects there developed roentgenologic evidence suggestive of gastritis and/or duodenitis during the preicteric or early icteric period of their experimentally induced infectious hepatitis lends support to the concept that the gastrointestinal tract may be involved in the disease.

The development of gastroscopic evidence of acute superficial gastritis during the acute phase of hepatitis, with subsidence during convalescence, in 3 out of 6 of these subjects furnishes further confirmatory evidence. It is of interest that there was no particular correlation between gastroscopic and roentgenologic evidence of change. Of the 3 men who had gastroscopic evidence of acute superficial gastritis, the roentgenographic examinations showed normality in 1 and gastroduodenitis in the second; the third man (V. W.) had the same appearance roentgenographically before and after ·inoculation, although he had evidence of change from normal mucosa to acute gastritis by gastroscope. Of the 3 men who showed no demonstrable change gastroscopically in the acute phase of disease, roentgenologic evidence of duodenitis developed in 1, and the other 2 had normal roentgenograms of the gastrointestinal region. There was also no particular correlation between the severity of symptoms such as anorexia, nausea and vomiting and the presence of roentgenographic or gastroscopic changes. Nevertheless, our findings indicate that gastric changes do occur in this disease.

13. Pöschl.[3] Knight.[4]

SUMMARY

1. Roentgenographic examinations of the stomach and duodenum were made on 21 human volunteers with experimentally induced infectious hepatitis. Twelve of these men were also examined before experimental inoculation.

2. Of the 9 men without previous control examination, 3 had roentgenographic evidence of gastritis and/or duodenitis during the course of hepatitis.

3. Of the 12 men who had previous control examination, 1 showed evidence of gastroduodenitis before inoculation. In 4 of the remaining 11 there developed roentgenologic evidence of gastritis and/or duodenitis during the early phase of disease.

4. Six of these men had gastroscopic examination before inoculation and during the acute and convalescent phases of disease. Of these, gastroscopic evidence of acute superficial gastritis, which receded during convalescence, developed in 3.

5. No particular correlation was found between roentgenologic and gastroscopic changes in human volunteers with experimentally induced infectious hepatitis.

6. The gastroscopic findings indicate that acute inflammation of the wall of the stomach is one of the lesions of the acute stage of infectious hepatitis. Evidences of this lesion may last into convalescence.

EPILEPTOGENIC EFFECTS OF PENICILLIN

An Experimental Study

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IN 1945 Johnson and Walker [1] reported the death of a hydrocephalic child into whose cerebral ventricles large amounts of penicillin had been injected for treatment of an infectious condition. In this child status epilepticus had developed after administration of penicillin. This observation led Walker and his associates to carry out experimental studies [2] in which they demonstrated that penicillin may produce convulsions when brought into contact with cerebral tissue under a variety of conditions and in several species of animals.

A similar investigation has been made in our laboratory, and it is the purpose of this paper to present its results.

METHODS AND RESULTS

Dogs weighing 7 to 12 Kg. were used in all experiments. When operative procedures were involved, they were carried out with the animals under anesthesia induced by intravenous administration of pentobarbital sodium as separate procedures. Administration of penicillin was done on another day and without anesthesia or other medication in all instances.

The accompanying table shows the incidence of convulsions in all groups of experiments.

1. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin: Note of Warning, J. A. M. A. **127**:217-219 (Jan. 27) 1945.

2. Walker, A. E., and Johnson, H. C.: Convulsive Factor in Commercial Penicillin, Arch. Surg. **50**:69-73 (Feb.) 1945. Walker, A. E.; Johnson, H. C., and Kollros, J. J.: Penicillin Convulsions: Convulsive Effects of Penicillin Applied to Cerebral Cortex of Monkey and Man, Surg., Gynec. & Obst. **81**:692-701 (Dec.) 1945.

The Epileptogenic Effects of Penicillin (0.1 cc. = 1,000 units)

Control Experiments, Isotonic Solution of Sodium Chloride

Dog No	Dose (Cc.) and Site	Convulsions
PO 16	0.2, cortex	0
PO 17	0.2, cortex	0
PO 22	0.4, cortex	0
PO 20	1.0, cistern	0
PO 21	1.0, cistern	0

Control Experiments, Autoclaved Penicillin

Dog No	Dose (Cc.) and Site	Convulsions
PO 7	15,000, cistern	0
PO 25	15,000, cistern	0

Subcortical Injection of Penicillin

Dog No.	Dose, Units	Convulsions
PO 8	250	0
PO 9	250	0
PO 9	350	0
PO 9	400	0
PO 9	450	+++
PO 9	500	+++
PO 8	500	+++
PO 19	500*	++
PO 26	500	+
PO 8	1,000	+++
PO 9	1,000*	+++++†
PO 14	1,000*	+++++†

Intracisternal Injection of Penicillin

Dog No.	Dose, Units	Convulsions
PO 6	5,000	+
PC 11	5,000	0
PO 12	5,000	0
PO 12	5,000	0
PO 7	7,500	+
PO 11	7,500	++
PO 12	7,500	++
PO 12	7,500	++++
PO 20	7,500	++
PO 26	7,500	+
PC 11	10,000	++
PO 25	10,000*	++++
PO 7	15,000	+++
PC 6	15,000*	+++++†
PC 15	15,000*	++++
PO 10	25,000	+++++†
PO 21	5,000	++
PO 20	7,500	++
PO 25	15,000*	++++
PO 27	5,000	0
PO 30	7,500	++++
PO 27	7,500	++++

Intraventricular Injection of Penicillin

Dog No.	Dose, Units	Convulsions
PO 23	3,000	+++
PO 13	5,000	++
PO 24	5,000	++
PO 7	5,000*	+
PO 18	5,000*	++++
PO 19	5,000*	+
PO 19	5,000*	++

* Crystalline penicillin.
† Fatal convulsions.

Control Experiments.—In five experiments isotonic solution of sodium chloride was injected into the cerebral cortex or into the cisterna magna in similar volume and with the same technic as the injections of penicillin to be described hereafter. No convulsions or other abnormal neurologic manifestations were observed in any experiment.

In two other observations a solution of 15,000 units of penicillin which had been autoclaved at 15 pounds (6.8 Kg.) of pressure for forty-five minutes was injected into the cisterna magna of each animal, without significant results.

Furthermore, in many experiments previously reported [3] kaolin and other irritating substances which had been placed on the brain did not induce convulsive seizures. In other unpublished experiments by Hodge and Pilcher, subcortical injection of the animal's own blood was not followed by irritative phenomena.

Subcortical Injection of Penicillin.—In twelve experiments a small metal cannula was screwed into an opening in the skull in the parietal area on the left side to such a depth that it exactly reached the surface of the dura. Subsequently, sodium penicillin in a solution containing 1,000 units per 0.1 cc. was injected 2 to 3 mm. beneath the cerebral cortex.[4] Dosages from 250 units to 1,000 units were employed. As shown in the table, convulsions did not occur in any animal receiving less than 450 units of penicillin. In all animals receiving this amount or more convulsions were produced. The seizures began from two to ten minutes following injection and showed a consistent pattern. Profuse salivation occurred first and was followed by facial twitching, usually contralateral to the place of injection but sometimes bilateral. There rapidly followed hard generalized clonic convulsions, rising to a crescendo of violence and then subsiding somewhat, only to wax again into a violent fit. Duration of the convulsions was from forty-five minutes to three hours except in 2 animals receiving 1,000 units of penicillin each, both of which remained in status epilepticus until death ensued twelve and twenty-four hours respectively after injection.

Frequent passage of urine and feces and a variable increase in the temperature of the body were usually observed.

Penicillin could not be demonstrated in the cerebrospinal fluid in these animals, nor was there a significant rise in the cerebrospinal fluid cell count. As indicated in the table, crystalline penicillin was employed in some of the experiments of this and other groups, with results identical with those obtained with commercial preparations of the drug.

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3. Meacham, W. F.; Angelucci, R.; Benz, E., and Pilcher, C.: Chemotherapy of Intracranial Infections: II. Clinical and Pathologic Effects of Intracranial Introduction of Sulfanilamide, Sulfathiazole and Sulfadiazine in Normal Dogs, Arch. Neurol. & Psychiat. **50**:633-651 (Dec.) 1943.

4. Knowledge of the length of the cannula and the length of the needle enabled the operator to gage the depth of injection accurately.

Injection of Penicillin Into the Cisterna Magna.—By the intracisternal route, the critical epileptogenic dose of a single injection of penicillin was 7,500 units (although in 1 animal mild convulsions developed after injection of 5,000 units). Convulsions were invariably produced by injection of 7,500 units or more and were extremely severe with larger doses (see the table). In 2 animals which received 15,000 units and 25,000 units respectively, the convulsions terminated fatally.
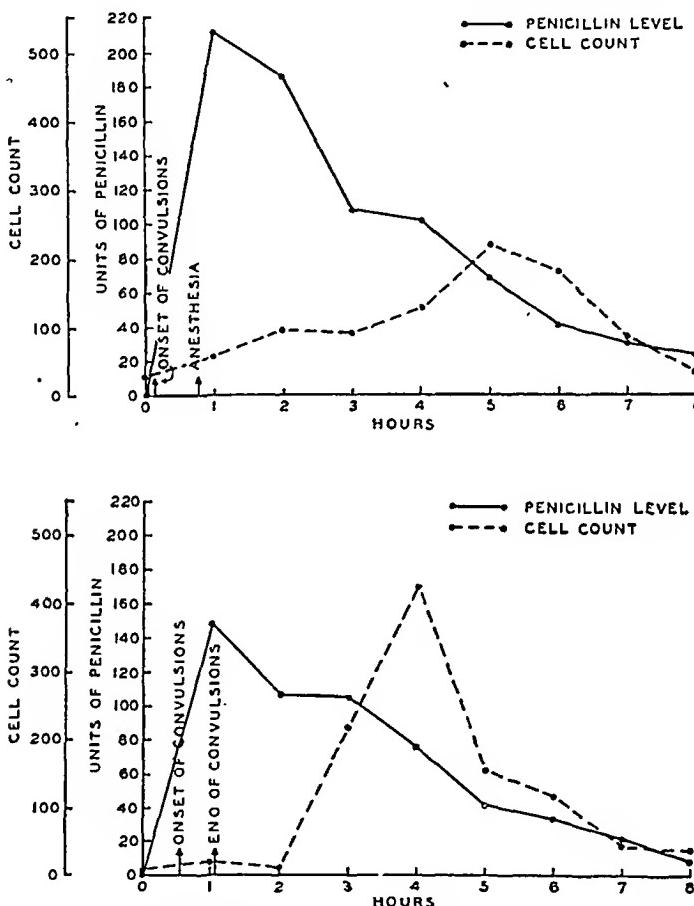
Chart 1.—The level of penicillin and the cell count in the cerebrospinal fluid following intracisternal injection of 7,500 units.

The seizures were slower in onset after intracisternal than after subcortical injection, usually beginning fifteen to thirty minutes after injection by the former route. The type of attacks and their duration were similar by the two routes.

That penicillin induces a pleiocytosis in the cerebrospinal fluid of dogs when injected intracisternally was reported by us in a previous communication,[5] and similar results were observed in human beings by

5. Pilcher, C., and Meacham, W. F.: The Chemotherapy of Intracranial Infections: III. The Treatment of Experimental Staphylococcic Meningitis with Intrathecal Administration of Penicillin, J. A. M. A. **123**:330 (Oct. 9) 1943.

Rammelkamp and Keefer.[6] Such a pleiocytosis also occurred in all the experiments herein reported. The increase in cells usually began within an hour after injection of penicillin and reached its maximum eight or nine hours later (charts 1 and 2). The height of the cell count bore no relationship to the onset, duration or cessation of convulsions.
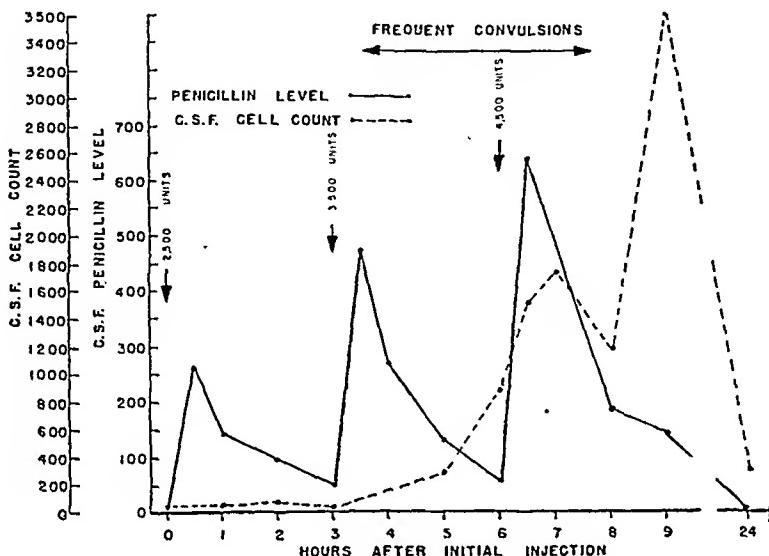
Chart 2.—The level of penicillin in the cerebrospinal fluid after intracisternal injection.
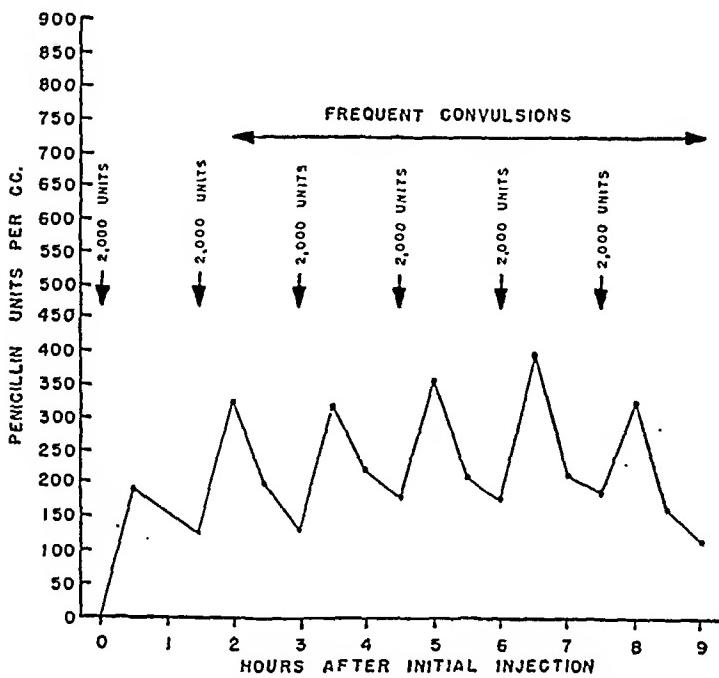
Chart 3.—The effects of frequent small intracisternal injections of penicillin.

6. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. 205: 342-350 (March) 1943.

Furthermore, the cellular response varied with the reaction of the individual animal independently of the dosage of penicillin.

However, there did seem to be a relatively constant "convulsive level" of the drug in the cerebrospinal fluid, as indicated by the cisternal injection of doses of increasing magnitude (chart 2) or of frequent small doses (chart 3). In these and other experiments, it seemed that a level of 300 or more units of penicillin per cubic centimeter in the cerebrospinal fluid would invariably be accompanied by convulsive seizures in the dog.[7] Once the critical level was reached, however,
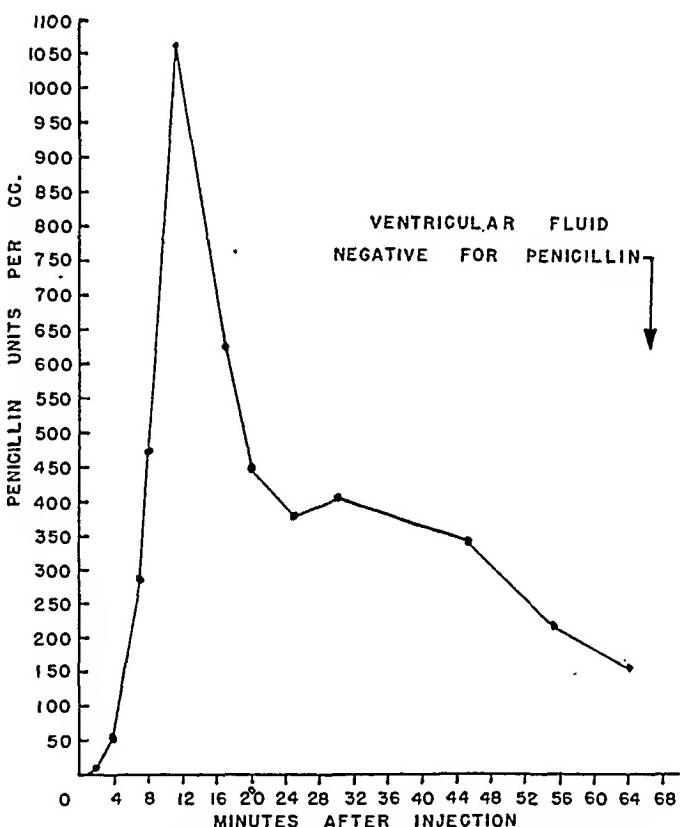
Chart 4.—The penicillin content of the cerebrospinal fluid over the cortex following injection of 10,000 units intracisternally.

convulsions might continue for some time after the level of the drug diminished (chart 3).

In several experiments it was possible to obtain specimens of cerebrospinal fluid from the subarachnoid space over the cerebral hemispheres after cisternal injection of penicillin. Assay of these specimens indicated extremely rapid diffusion of the drug over the cerebral cortex, a high level being reached in ten to twelve minutes (chart 4). These experi-

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7. The graphs in chart 1 do not show the maximum level of penicillin, since the first specimens indicated were obtained one hour after injection.

ments also showed that penicillin injected into the cistern did not enter the ventricular system in detectable amounts.

Injection of Penicillin into the Lateral Ventricle.—Because of the difficulty of ventricular puncture in the normal dog, a series of animals was prepared by injection of lampblack into the cisterna magna, which induced a moderate degree of hydrocephalus within six to eight weeks. In these dogs it was possible to make injections into the ventricles with certainty and without significant trauma. Despite the irritating effects of the lampblack, its wide distribution in the subarachnoid space and the extensive fibrosis induced by it in the leptomeninges, none of the animals had convulsive seizures prior to the injection of penicillin.
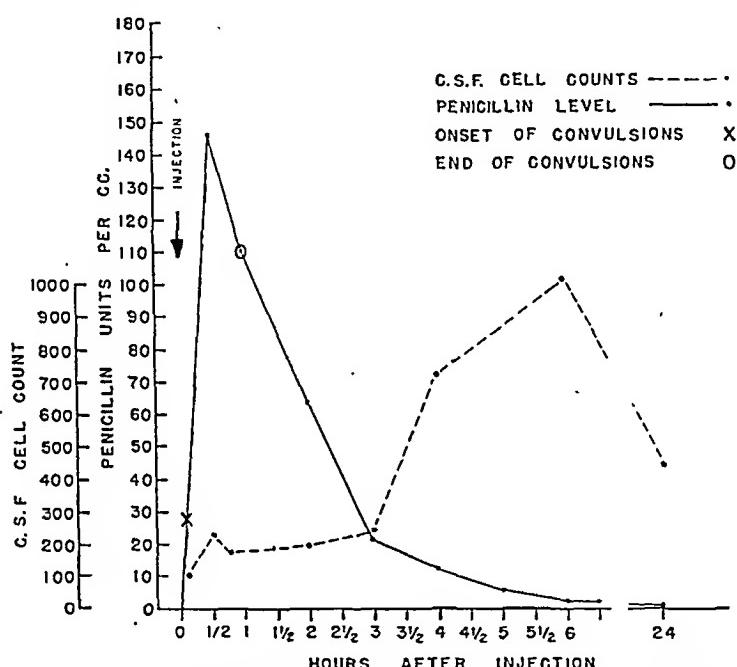
Chart 5.—The level of penicillin in the cisternal fluid, the cerebrospinal fluid cell count and the time of convulsions following intraventricular injection of 5,000 units.

In seven experiments on such hydrocephalic dogs, penicillin was injected into the lateral ventricle in doses of 3,000 to 5,000 units (see the table). In all instances convulsions developed within four to ten minutes. As would be expected, the drug appeared promptly in the cisternal fluid and the usual cellular reaction occurred (chart 5).

<center>COMMENT</center>

That penicillin can produce convulsions in the dog in the circumstances existing in our experiments is clear. Great caution is necessary, however, in interpreting these results in terms of possible harmful effects of the intrathecal or intracerebral use of penicillin clinically.

The critical epileptogenic dose of 7,500 units for a dog weighing 10 Kg. is equivalent to a dose of 52,500 units for a human being weighing

70 Kg. Although doses exceeding the latter amount have been reported to have been employed in a number of clinical cases, such dosage is far in excess of that usually advised. Further, it is true that dogs seem to be particularly susceptible to epileptogenic agents of various types. That the effects of penicillin are obtainable in other species is shown by the observations of Walker and Johnson.[2]

In our opinion, the experiments reported herein constitute a warning against excessive doses of penicillin by intrathecal administration, but they should not be construed as indicating that judicious intrathecal injection of penicillin is contraindicated.

SUMMARY

In dogs, large doses of penicillin injected into the cerebral cortex, into the cisterna magna or into the lateral ventricle produced violent and sometimes fatal convulsions.

The dosage required to produce convulsions varied according to the route of administration.

A critical level of 300 units of penicillin per cubic centimeter in the cerebrospinal fluid was necessary for the production of convulsions by intracisternal injection.

Book Reviews

Gastro-Enterology (in Three Volumes). By Henry L. Bockus, M.D., and Colleagues at the University of Pennsylvania Graduate School of Medicine. Volume III: Diagnosis and Treatment of Disorders of the Liver, Gallbladder, Biliary Tract and Pancreas. Intestinal Parasites and Secondary Gastro-Intestinal Disorders. General Index. Price, $35 per set of 3 volumes and separate desk index. Pp. 1,091, with 115 illustrations. Philadelphia: W. B. Saunders Company, 1946.

Volume 3 of this work is devoted to a consideration of diseases of the liver, biliary tract and pancreas and to parasitology and secondary gastrointestinal disturbances. As in the other volumes, there are preliminary chapters on the anatomy and physiology that are concerned with the various subjects. These are up to date and well documented. In the general discussion of disease syndromes, one finds much to commend and little to criticize. It is unfortunate that the section on infectious hepatitis was written just prior to the publication of so many studies in this field. The possibility that arsenical hepatitis may be due to transmission of the virus of hepatitis by contaminated syringes is, for instance, hardly mentioned. There is an excellent discussion of cirrhosis of the liver and of the metabolic diseases involving that organ.

The diseases of the gallbladder and the biliary passages are considered in great detail in some well written chapters. One may disagree with the authors in regard to the diagnostic value of duodenal intubation, but one can find no fault with their general presentation of the subject.

The section on pancreatic disease is particularly good and complete. One of the most valuable sections of the book has to do with gastrointestinal disturbances which are secondary to systemic disease and psychiatric conditions. This reviewer knows of no other work in which these subjects are so completely considered as in the volume under consideration.

The whole work is well illustrated, and there are many valuable tables and illustrations, such as the table on page 197, which presents in practical form the differential diagnosis between obstructive and hepatic cellular jaundice. There is an excellent chapter on the physiologic basis and interpretation of tests of hepatic function. The entire work is well documented with an excellent bibliography, and it has a general index. These three volumes should make an exceedingly valuable reference work for any one interested in the field of gastroenterology.

Skin Diseases, Nutrition and Metabolism. By Erich Urbach, M.D., and Edward B. LeWinn, M.D. Price, $12. Pp. 634, with 266 illustrations. New York: Grune & Stratton, Inc., 1946.

This book, the reviewer believes, represents a noteworthy attempt to relate disorders of the skin to more general disturbances of nutrition and metabolism. While much of the material will be found in other dermatologic treatises, the important thing here is that the author tries to get away from the old "botanical" classifications of dermatoses, made by inspection alone, and to penetrate literally as well as figuratively beneath the skin. To make this clear one may mention some of the chapter headings: "Influence of Diet on Metabolism of the Skin," "Allergy as a Cause of Skin Diseases" and "Dermatoses Due to Diseases of Liver and Pancreas." The book is well printed and illustrated, and there are numerous references. It should mark a step in advance in relating dermatology to internal medicine.

Electrocardiography in Practice. By Ashton Graybiel, M.D., and Paul D. White, M.D. Second edition. Price, $7. Pp. 458, with 323 illustrations. Philadelphia and London: W. B. Saunders Company, 1946.

Electrocardiography may be approached from two standpoints. First, there is the use and interpretation of the tracings by the general physician. He must know the elements of electrocardiographic interpretation and be able to recognize the changes of important conditions such as auricular fibrillation or complete heart block. Second, there is the study of the meaning in cardiac physiology of more esoteric changes in the electrocardiogram, and here one enters the field of research and the domain of the expert. While the present work is thoroughly done and deals comprehensively with the subject, its main purpose is still to help and instruct the physician in understanding and interpreting tracings. The general introductory matter, the abundant illustrations and the clinical notes all help in carrying out this purpose, and the book is to be highly recommended as an instructive and readable treatise, comprehensive enough but not going into controversial matters enough to confuse the practitioner.

A Manual of Tuberculosis: Clinical and Administrative. By E. Ashworth Underwood, M.D. Third edition. Price, $4.50. Pp. 540, with 88 illustrations. Baltimore: The Williams & Wilkins Company, 1945.

This well written manual of handy size but containing over five hundred pages describes in clear but simple form the subject of tuberculosis. The general principles of infection, clinical features and general treatment are followed by discussions of special forms of tuberculosis, epidemiology, laboratory methods and related subjects. The discussions seem to represent sound current opinion. The volume is handsomely printed, and there are numerous illustrations of pathologic material, roentgenograms, apparatus and equipment for sanatoriums.

Diseases of the Retina. By Herman Elwyn, M.D. Price, $10. Pp. 593, with 170 illustrations. Philadelphia: The Blakiston Company, 1946.

This new volume is divided into eight sections in which the author discusses vascular disturbances and malformations, hereditary degenerations, inflammatory disease, developmental anomalies, detachment, tumors and injury of the retina due to radiation. The clinical picture, ophthalmoscopic appearance, pathogenesis, pathologic changes, course and treatment are considered, and there are excellent illustrations of both the funduscopic and the microscopic appearance of all the commoner and many of the unusual conditions involving the retina. The section on degenerative changes on a hereditary basis is particularly comprehensive and places in one volume much material which has previously been available only from a number of sources.

By avoiding controversy, particularly as to the pathogenesis of the conditions, the author has condensed a huge amount of information in relatively few pages. The bibliography is representative, and the printer has done an excellent job.

Motor Disorders in Nervous Diseases. By Ernst Herz, M.D., and Tracy J. Putnam, M.D. Price, $3. Pp. 184. New York: King's Crown Press, 1946.

This small book is a "descriptive syllabus for study before and after viewing a projection" of teaching films prepared in the Department of Neurology at Columbia University and the Neurological Institute, New York. Even without the films, the clear, simple text and the two hundred and fifty well chosen illustrations constitute a brief atlas of the commoner motor neurologic disorders and a useful manual of clinical methods for their demonstration. Controversial matters are eschewed, and only elementary facts are presented. Somewhat trite for the well versed neurologist, the volume is nevertheless a worthy compendium of what the physician can and should know about the subject, as well as a valuable primer for the student.

ERUPTIVE FEVER WITH INVOLVEMENT OF THE RESPIRATORY TRACT, CONJUNCTIVITIS, STOMATITIS AND BALANITIS

An Acute Clinical Entity, Probably of Infectious Origin; Report of Twenty Cases and Review of the Literature

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DURING the past several years, 20 cases of an unusual disease syndrome, which has had some mention in the literature of the past sixty years, have been observed at a military installation. The syndrome has been described under a variety of appellations such as eruptive fever with stomatitis and ophthalmia, erythema exudativum multiforme of Hebra, erythema or herpes iris conjunctivae, ectodermosis erosiva pluriorificialis and Stevens-Johnson syndrome. Such a terrifying array of unfamiliar and difficult names suggests, perhaps, why ·this disease remains an unknown and undiagnosed entity to most physicians. However, after one has seen a typical case the various clinical features fall into a rather easily recognized pattern which is difficult to mistake thereafter.

This condition is an acute, systemic, frequently febrile disease running a self-limited course of a few days to several weeks and involving, to varying degrees, the respiratory tract, skin and mucous membranes, chiefly those of the eyes, mouth and urethral meatus. The onset occurs usually with a cold, cough, malaise and sore throat, followed frequently by fever. After a few days an eruption appears in the mouth, characterized by clear vesicles, which usually rupture within twenty-four to forty-eight hours and are replaced by a gray-white pseudomembrane. The lesions usually become secondarily infected and may remain patchy or become confluent and extremely extensive. Frequently, conjunctivitis appears at the same time and may progress to involve the deeper structures of the eye, resulting in partial or total blindness. Bronchitis occurs in the majority of cases and may go on occasionally to bronchopneumonia. These early manifestations are followed later by erythema multiforme, usually of the iris type, with a predilection for the hands and feet but occasionally generalized, and balanitis which originates in or around the urethral meatus. Recovery is complete except for the rare severe ocular

TABLE 1.—*Résumé of Cases*

Author	Age, Yr.	Sex	Prodromal Symptoms	Skin	Oropharynx
Blair (1904)	12	Male	?	Generalized maculopapular rash, later iris in type, then pustular	Pseudomembranous stomatitis, with ulceration
Barkan (1913)	?	Male	?	Generalized erythema multiforme, with hemorrhagic blebs	Diffuse stomatitis, with vesicles and ulcers
Stark (1918)	6	Female	Fever	Generalized erythema multiforme, later iris in type	Diffuse stomatitis
Stevens and Johnson (1922)	8	Male	Sore throat, malaise	Generalized erythema multiforme	Vesicles followed by patchy erosions
	7	Male	Conjunctivitis	Generalized macular rash, later hemorrhagic sealing	Normal
Butler (1922)	16	Male	?	Iris lesions on hands and feet	Diffuse stomatitis, with vesicles and erosions
Wheeler (1929)	8	Male	Cold, malaise and sore eyes and mouth	Generalized macular rash	Scattered membrane in mouth and pharynx
Smith (1929)	9	Male	Cough, malaise and generalized itching rash	Generalized maculopapular rash, with vesiculation and erosion	Pronounced stomatitis, with vesiculation
Rutherford (1929)	2	Male	Cold and sore throat	Erythema multiforme on face and forearms	?
Bailey (1931)	39	Male	Cold, cough, sore throat, malaise and fever	Generalized erythema multiforme, with hemorrhage and crusting	Diffuse pseudomembrane; crusting of lips
	9	Male	Sore throat, fever, malaise and rash	Generalized erythema multiforme, with hemorrhage and vesiculation	Diffuse ulceration and hemorrhage, then a diffuse pseudomembrane
	7	Male	Malaise, pain in extremities and rash	Generalized maculopapular rash, later hemorrhagic	Sore; no mention of findings
Ginandes (1935)	5	Male	Malaise, fever and rash	Generalized erythema multiforme, later vesicular, bullous, and hemorrhagic	Vesicles, then pseudomembrane with ulcers; gums involved
Klauder (1939)	7	Male	Cold, fever and sore eyes and mouth	Normal	Moderate stomatitis, with crusting of lips
	13	Male	Cold, cough, malaise and sore mouth and throat	Iris lesions on palms and soles	Vesicles followed by confluent pseudomembrane
Laszlo (1939)	23	Male	Cold and sore eyes and mouth	Normal	Pseudomembrane (also present in nose)
Rosenberg and Rosenberg (1940)	11	Male	Cold, cough, fever, malaise and sore mouth	Erythema multiforme on arms and legs	Pseudomembrane; gums swollen and hemorrhagic
Ageloff (1940)	4	Female	Fever and rash	Generalized erythema multiforme with iris lesions and bullae	Diffuse ulceration and crusting of lips
Givner and Ageloff (1941)	23	Male	Fever and sore eyes and mouth	Generalized erythema multiforme with iris lesions and bullae	Diffuse pseudomembrane
Levy (1943)	27	Male	Sore throat and rash	Iris lesions	Patchy pseudomembrane
Murphy (1944)	22	Male	Cough, malaise and sore mouth	Iris lesions on soles, palms and extremities	Vesicles, then confluent pseudomembrane

Eyes	Genital Region	Lungs	White Blood Cell Count	Duration of Fever	Bacteriology	Comment
Conjunctivitis followed by diphtheritic membrane	Membrane over glans	Broncho-pneumonia	?	4 to 6 wk.	Mixed pyogenic organisms in mouth and eyes	Six recurrences; cervical adenopathy on one occasion and involvement of anus and larynx on another
Pseudomembranous conjunctivitis leading to corneal opacities and blindness	Bloody urethral discharge	?	?	?	?	Previous attack 6 mo. before with stomatitis and conjunctivitis
Chronic pseudomembranous conjunctivitis ending in scars and corneal opacities	?	?	?	?	?	Residual blindness
Purulent conjunctivitis ending in left corneal ulceration and scarring	Normal	Normal	4,600	24 days	Mixed pyogenic organisms in mouth and eyes	Partial loss of vision
Purulent conjunctivitis, corneal ulcers and destruction of both globes	Normal	Broncho-pneumonia	?	5 wk.	?	Complete blindness
?	?	?	?	?	?	Fourth attack; in next attack had stomatitis plus similar lesions in esophagus and rectum
Purulent conjunctivitis, then bilateral corneal ulceration and scarring	?	?	7,000	?	Mixed pyogenic organisms in eyes	Residual partial blindness
Purulent conjunctivitis	?	Broncho-pneumonia	11,000	7 days	Hemolytic streptococci in sputum	Fatal in 7 days; autopsy revealed severe diphtheritic type of inflammation of skin, mouth and respiratory tract
Recurring pseudomembranous conjunctivitis followed by deep infection of both bulbs	Normal	Bronchitis	?	60 days	Mixed pyogenic organisms in eyes	Enucleation of both eyes
Purulent conjunctivitis, then corneal ulceration and scarring	Normal	?	?	3 wk.	Usual organisms in mouth	Residual partial blindness
Purulent conjunctivitis with pseudomembrane, then corneal ulceration and scarring	Normal	Bronchitis	Normal	3 wk.	Staph. aureus in mouth and eyes; culture of the blood sterile	Complete blindness
Purulent conjunctivitis, then corneal scarring bilaterally	Normal	Normal	16,000	18 days	Smears negative for diphtheria bacilli in eyes and throat; culture of the blood sterile	Complete blindness
Purulent conjunctivitis, then endophthalmitis on the left side	Normal	Normal	6,000	10 days	No Vincent's organisms; mixed pyogens in eyes and mouth; cultures of the blood negative	Enucleation of left eye
Purulent conjunctivitis	Normal	Normal	?	7 days	?	Uneventful recovery
Purulent conjunctivitis	Vesicles on glans	Bronchitis	14,800	14 days	No Vincent's organisms in the mouth	Uneventful recovery
Purulent conjunctivitis with pseudomembrane	Pseudomembrane on glans	Normal	16,700	10 days	No Vincent's organisms in the mouth; Staph. albus in the eyes	Uneventful recovery
Purulent conjunctivitis	Normal	Purulent bronchitis	22,000	21 days	No Vincent's organisms in the mouth	Residual bronchiectasis and pulmonary fibrosis
Purulent conjunctivitis	Diffuse vaginal lesions	Normal	20,400	14 days	No Vincent's organisms in the mouth	Biopsy of skin revealed specific inflammation
Pseudomembranous conjunctivitis	Normal	?	?	?	Staph. aureus in eyes; cultures of vesicle fluid in yolk sacs negative	Vesicular lesions in nose; desquamation of nails
Normal	Normal	Normal	9,600	?	?	Uneventful recovery
Mucopurulent conjunctivitis	Vesicles on glans	Normal	13,000	5 days	Eosinophils in oral vesicles	Pseudomembranous rhinitis also present; uneventful recovery

complications, but a patient may have one or more recurrences, as many as fourteen having been reported.

<div align="center">LITERATURE</div>

Twenty-two cases were compiled from sources in the English language. Those reported in foreign literature were not covered extensively (table 1). Von Hebra,[1] in 1866, is generally credited with first having separated erythema exudativum multiforme from the heterogeneous erythemas. This he regarded as a clinical entity characterized by fever, constitutional symptoms and cutaneous lesions. The last were described as dark blue or purplish erythematous macules, later becoming papular or nodular or developing central clearing (erythema iris) or central vesiculation (herpes). In the average case the eruption was present on the dorsa of the hands and feet, but it could spread to the trunk and face in the severer instances. There was a seasonal incidence—in spring and fall—and a tendency to relapse. Later writers enlarged on Hebra's concept. In 1876 Fuchs[2] called attention to ocular involvement by reporting a case with pseudomembranous conjunctivitis associated with a generalized eruption of the herpes iris type and vesicles in the buccal mucous membrane, under the term "herpes iris conjunctivae." The conjunctival involvement ranges from a mild inflammation to a severe membranous form which may lead to ulceration of the cornea and subsequent loss of vision. Kaposi[3] in 1893, in stressing the oral involvement, said:

With the appearance of the skin eruption there may be seen similar lesions, reddish spots, papules and vesicles on the mucous membrane of the mouth and throat over which the epithelium rapidly becomes turbid and is elevated in the form of membranes and shreds so that painful wounds arise. Rarely, the epiglottis, larynx, vulvovaginal and urethral mucous membranes are attacked.

In his book "Histopathology of Diseases of Skin," in 1896, Unna[4] echoed Hebra's criteria for diagnosis. An epidemic form of the disease in Turkey was reported by von Duhring in 1896.[5]

In the American literature Whitehouse[6] in 1900 gave the first fairly good description of the subject while discussing erythema exudativum

1. von Hebra, F.: Diseases of Skin, London, New Sydenham Society, 1866, vol. 1.

2. Fuchs, E.: Herpes Iris Conjunctivae, Klin. Monatsbl. f. Augenh. **14**:333-351, 1876.

3. Kaposi, M.: Pathologie und Therapie der Hautkrankheiten, ed. 4, Vienna, Urban & Schwarzenberg, 1893.

4. Unna, P. G.: Histopathology of Diseases of Skin, translated by N. Walker, edited by C. H. Fagge, New York, Macmillan & Co., 1896, p. 21.

5. von Duhring, E.: Bietrag zur Lehre von den polymorphen Erytheman, Arch. f. Dermat. u. Syph. **35**:211-323, 1896.

6. Whitehouse, H.: Twentieth Century Practice of Medicine, New York, William Wood & Company, 1900, vol. 5, p. 50.

multiforme of the herpes iris type. He reported that the disease might begin on and be confined to a mucous membrane and emphasized the involvement of the mouth and pharynx and associated pain and dysphagia.

Blair[7] in 1904 published a report of a classic case which leaves little to be added. He emphasized the tendency to recurrence. His patient was a 12 year old boy whose illness began in May with many "sores" covering one third of the buccal, sublingual, gingival and palatal surfaces. These were ulcerated but covered with a diphtheria-like membrane. Salivation was pronounced, and swallowing was difficult. On the sixth day a rash and conjunctivitis appeared. The temperature was high and continued so. The cutaneous lesions became iris type or even bullous, hemorrhagic and, finally, crusted. A "diphtheria-like" condition developed in the eyes. The illness lasted one month, and recovery was accompanied with scarring in the eyes and mouth. The next two attacks occurred in May 1900 and June 1901. The fourth attack, in March 1903, lasted six weeks and was the severest. This time, confluent membrane formed in the mouth and then spread to the nasal passages, nasopharynx, larynx and, eventually, trachea, simulating laryngeal diphtheria. The conjunctivas became involved, and then membrane formed around the anus, glans penis and urethra. On the eighth day successive crops of generalized iris lesions began to appear. In the fourth week bronchopneumonia developed, lasting five or six days. Thereafter, convalescence and recovery were uneventful. The cutaneous lesions healed but left a coppery discoloration behind, which persisted for months. The fifth and sixth attacks occurred in the same year but were much milder. (No mention is made of the drugs used.)

In a brief report, Barkan[8] in 1912 reported a case of the condition in a male, age not mentioned, who recovered from two attacks, the first with conjunctivitis and stomatitis and the second, fifteen months later, with fever, generalized erythema multiforme, stomatitis, bloody urethral discharge and severe conjunctivitis ending in bilateral corneal opacities. A similar condition in a 6 year old girl was reported by Stark[9] in 1918, resulting in membranous conjunctivitis lasting four years and leaving residual corneal opacities.

In 1922 Stevens and Johnson,[10] under the impression that they were describing a new entity, reported 2 cases under the diagnosis of eruptive fever with stomatitis and ophthalmia. However, their findings did not

7. Blair, L. E.: A case of Recurring Membranous Stomatitis, Associated with Erythema Exudativum Multiforme (Hebra), M. Rec. **65**:729-732, 1904.

8. Barkan, H.: Herpes Iris of the Conjunctiva: Report of a Case, Arch. Ophth. **42**:236-240, 1913.

9. Stark, H. H.: Membranous Conjunctivitis of Over Four Years' Duration, Am. J. Ophth. **1**:91-94 (Feb.) 1918.

10. Stevens, A. M., and Johnson, F. C.: New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child. **24**:526-533 (Dec.) 1922.

differ significantly from those of Whitehouse, Blair, Barkan, Stark and others. The cutaneous lesions were generalized in both cases and consisted of red to purple macules, changing to papules, which later became hemorrhagic (in 1) and then crusted and cleared, leaving faint brownish pigmentation for some time. The rash in the second case lasted for five weeks, the palms and soles being involved, which is unusual. Lesions in the mouth were absent in case 2 and apparently of little significance in case 1. Ocular involvement was severe, starting with purulent conjunctivitis and ending with a corneal scar in case 1 and panophthalmitis in case 2, with rupture of both globes and total blindness. From an etiologic standpoint, there was no history of ingestion of drugs. Smears and cultures of material from the mouth and eyes revealed mixed infection. Cultures of the blood were sterile in case 1. The authors stated:

Erythema multiforme, from some unknown toxic cause, was proposed as a diagnosis, but this is unsatisfactory from the character and distribution of the lesions, the lack of subjective symptoms, the prolonged high fever, and the terminal heavy crusting. . . . Finally, we have been impressed by the striking picture presented by these cases. Here is a syndrome of dramatic onset, with fever, conjunctivitis and cutaneous eruption. The child is prostrated, the mouth and tongue are inflamed and raw, the eyelids are swollen and pus streams from the eyes. There is a course of three or more weeks of high fever, with leukopenia. The eruption, unlike any hitherto described, comes out progressively, for two weeks or more, matures and resolves in horny crusts, in the order of its appearance. The temperature falls with this resolution of the skin lesions. This syndrome suggests strongly an infectious disease of unknown etiology. We believe that this condition deserves to be considered a definite clinical entity.

Butler [11] in 1922 observed a 16 year old boy in four attacks of diffuse stomatitis characterized by vesicles and diffuse erosion. On one occasion similar lesions were present in the esophagus and rectum. Involvement of the skin was an accompanying finding only once, when iris lesions appeared on both surfaces of the hands and feet.

In 1925 Baader [12] described 7 cases of what he termed "dermatostomatitis." These cases apparently fall into the group under discussion, since there were high temperature, systemic symptoms, conjunctivitis, balanitis, rhinitis and severe membranous stomatitis. The cutaneous lesions were frequently of the iris type, but the author hesitated to place his cases in the group of cases of eruptive fever since the eruptions did not occur on the sites of predilection described by Hebra.

An instance of severe purulent conjunctivitis followed by corneal ulceration and finally scarring was reported by Wheeler [13] (1929) in

11. Butler, J.: Erythema Multiforme Confined to Mucous Membranes, Arch. Dermat. & Syph. 6:1-5 (July) 1922.

12. Baader, J.: Dermatostomatitis, Arch. f. Dermat. u. Syph. 149:261-268, 1925.

13. Wheeler, J. M.: Destructive Purulent Ophthalmia Accompanying an Eruptive Fever with Stomatitis: Report of a Case, Tr. Am. Acad. Ophth. 34:179-180, 1929.

an 8 year old boy. The onset was respiratory in type and was followed by a generalized macular eruption and the appearance of scattered, patchy pseudomembrane in the mouth and pharynx.

In 1929 an unusual fatal case of erythema multiforme in a 9 year old boy was reported by Smith.[14] The illness ran its course in six days, with high temperature, a rapidly spreading generalized maculo-papular eruption resulting in vesicles and bullae up to 5 cm. in diameter, oral involvement similar to that of the skin, severe purulent conjunctivitis and, finally, bilateral bronchopneumonia. There was no known exposure to contagion or drugs. There were 11,200 leukocytes per cubic millimeter of blood, culture of the blood was sterile and the sputum contained a type II pneumococcus. Findings at autopsy were inconclusive. The diagnosis of erythema multiforme was considered most likely.

Ophthalmologists have long been interested in membranous conjunctivitis, seeing it in association with a variety of contagious and dermatologic diseases, including erythema multiforme.[14a] Bailey [15] (1931), in reporting 3 cases of the latter with residual partial or complete blindness, pointed out as the main clinical features: (1) an onset characteristic of acute infection, with chilly sensations, fever, headaches, anorexia, malaise and frequent pain in the joints; (2) decided inflammatory changes in the conjunctivas and corneas, eventuating in serious visual impairment and often in total destruction of the bulb; (3) an intense pseudo-membranous inflammation of the various surfaces of the lips, tongue, palate, oropharynx and, occasionally, of the nares, larynx, bronchi and even the vagina and (4) widespread polymorphous eruption of the skin. In discussing the ocular complications, Bailey emphasized the insidious progression from hyperemia to destruction of tissue, often necessitating enucleation.

Ginandes [16] in 1935, while reporting a typical case, endeavored to break down Stevens and Johnson's rigid insistence on the type of the cutaneous lesions and other characteristics of the disease. He insisted:

The slight variations in the nature and duration of the cutaneous lesions and the difference in the degree of buccal and ocular involvement should not prevent one from recognizing the identity of the more important clinical manifestations. Dermatologists have frequently emphasized that the character of the cutaneous

14. Smith, C. A.: Unusual Case of Erythema Multiforme, Tr. Univ. Michigan Pediat. & Infect. Dis. Soc., 1929, pp. 63-67.

14a. Rutherford, C. W.: Membranous Conjunctivitis with Loss of Eyeballs: Report of Cases, J. A. M. A. 93:1779-1784 (Dec. 7) 1929.

15. Bailey, J. H.: Lesions of Cornea and Conjunctiva in Erythema Exudativum Multiforme (Hebra): Report of Three Cases with Grave Ocular Sequelae, Arch. Ophth. 6:362-379 (Sept.) 1931.

16. Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia: Atypical Erythema Exudativum Multiforme (Stevens-Johnson), Am. J. Dis. Child. 49: 1148-1160 (May) 1935.

lesions is markedly altered by the degree of exudation. Thus, a certain eruptive fever that may cause macular or papular lesions in one patient may give rise to vesicular or bullous lesions in another. . . . Similarly the severity of the ocular manifestations, as has been pointed out by Rutherford, may simply be the expression of the degree of reaction.

It is significant that heretofore such cases have been described in the main by the dermatologists and the ophthalmologists. In the last six years Edgar and Syverton,[17] Laszlo,[18] Rosenberg and Rosenberg,[19] Ageloff,[20] Givner and Ageloff,[21] Levy [22] and Murphy [23] have reported cases of this syndrome. It is interesting to note that Murphy considered the disease to be "definitely in the pediatric sphere."

Ectodermosis erosiva pluriorificialis, an old and still confusing term for this disease, originating with Fiessinger and Rendu [24] in 1917, was reintroduced by Klauder [25] in 1937. He considered it to be a variant of erythema multiforme and traced its similarity to human foot and mouth disease but was unable to show any relationship by experimental means. He covered the literature thoroughly and expressed the opinion that erythema exudativum multiforme as described by Hebra is probably a specific disease of relapsing nature. He subdivided the disease into several clinical varieties, mainly the Hebra type, involving the skin pri-

17. Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis: Report of Two Cases in Children with Certain Observations on Histopathology and Animal Inoculation, J. Pediat. **12**:151-159 (Feb.) 1938.

18. Laszlo, A. F.: Acute Pseudomembranous Infections Involving Eye, Mouth, Throat and Urethra, Laryngoscope **49**:208-216 (March) 1939.

19. Rosenberg, L., and Rosenberg, J.: Erythema Exudativum Multiforme (Hebra), with Conjunctivitis and Stomatitis, Arch. Dermat. & Syph. **41**:1066-1072 (June) 1940.

20. Ageloff, H.: Erythema Multiforme Bullosum with Involvement of Mucous Membranes of Eyes and Mouth (Stevens-Johnson Disease): Report of Case, New England J. Med. **223**:217-219 (Aug. 8) 1940. Andrews, G. C.: Diseases of Skin, Philadelphia, W. B. Saunders Company, 1938.

21. Givner, I., and Ageloff, H.: Stevens-Johnson Disease with Complete Visual Recovery, New York State J. Med. **41**:1762-1765 (Sept. 1) 1941.

22. Levy, A. T.: Erythema Multiforme Bullosum with Involvement of Mucous Membranes of Mouth (Stevens-Johnson Disease), J. Am. Dent. A. **30**:287-288 (Feb.) 1943.

23. Murphy, R. C., Jr.: Eruptive Fever Involving Mouth and Eyes (Stevens-Johnson Disease), New England J. Med. **230**:69-71 (Jan. 20) 1944.

24. Fiessinger, N., and Rendu, R.: Sur un syndrome caracterise par l'inflammation simultanée de toutes les muqueses externes coexistant avec uno eruption vesiculeuse des quatre membres, non douloureuse et non recidivante, Paris méd. **23**:54-58, 1917.

25. Klauder, J. V.: Ectodermosis Erosiva Pluriorificialis: Its Resemblance to the Human Form of Foot and Mouth Disease and Its Relation to Erythema Exsudativum Multiforme, Arch. Dermat. & Syph. **36**:1067-1077 (Nov.) 1937.
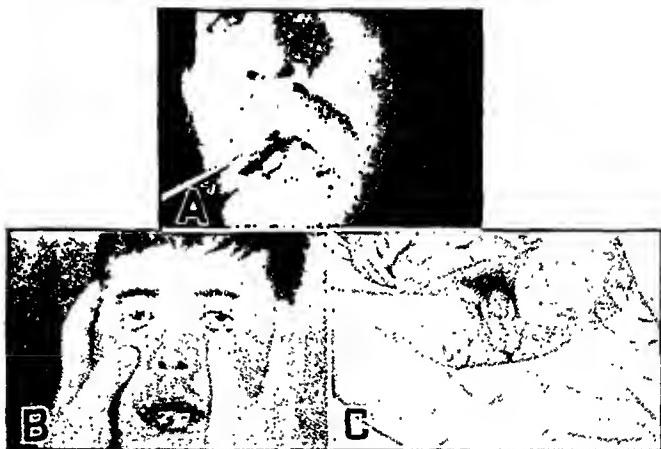
Fig. 1.—*A*, late pseudomembrane on the tongue. *B*, crusting of the lips, ass‑
ated with conjunctival injection. *C*, iris lesions on the thighs.
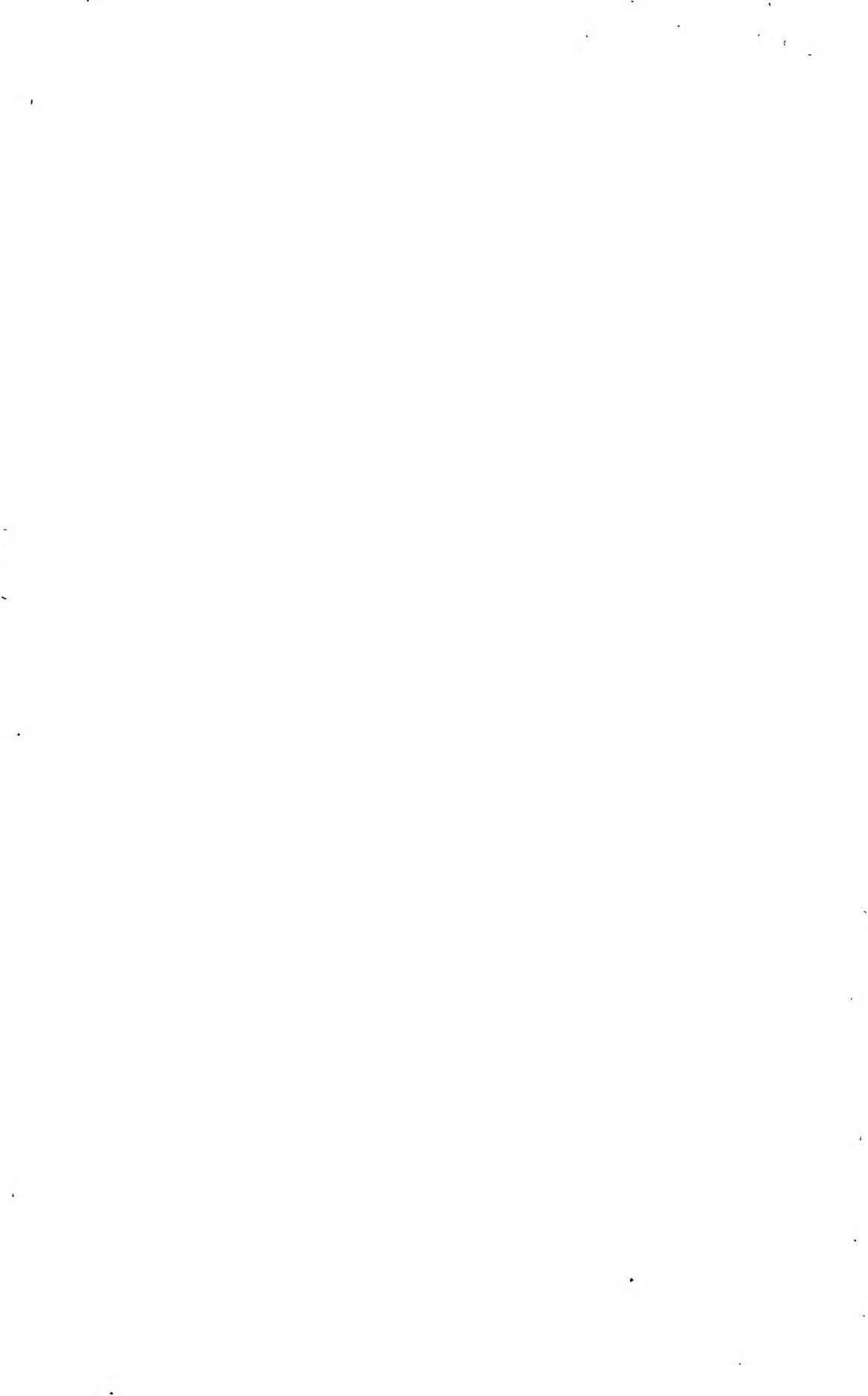
TABLE 2.—*Scope of Erythema Exudativum Multiforme* (Reprinted from Klauder [25])

Erythema Exudativum Multiforme (Hebra)	Toxic Erythema Resembling Erythema Exudativum Multiforme
(Probably a specific disease, relapsing, involving the skin and mucous membranes. Cutaneous lesions: erythema of variable shape, papules, nodules, vesicles, bullae and hemorrhagic macules. Distinctive lesions: annular erythema with central clearing, erythema iris and herpes iris)	(A cutaneous reaction to various causes. Cutaneous lesions: erythema, vesicles, bullae, angioneurotic edema, urticaria and purpura)

Types Affecting the Mucous Membranes

Hebra Type	Ocular	Nasal	Oral	(Ectodermosis Erosive Pluriorificialis)	Severe Type (Stevens-Johnson)
Commonest; eruption favors areas of predilection, with or without constitutional symptoms or involvement of mucous membrane	Vesicles; simple inflammation; membranous conjunctivitis	Simple inflammation	Vesicles; erosions; diffuse stomatitis	Fever; constitutional symptoms; vesicular eruption on hands and feet; conjunctivitis; stomatitis and rhinitis	Fever; constitutional symptoms: hemorrhagic macules; crusting; scaling; stomatitis; membranous conjunctivitis; leukopenia

Toxic Erythema Resembling Erythema Exudativum Multiforme:

1. Systemic infection
2. Drug eruption
3. Serum sickness associated with visceral disease
4. Osler's erythema group
5. Libman-Sacks syndrome
6. Toxic erythema described as:
   (a) Urticaria perstans annulata et gyrata
   (b) Erythema multiforme perstans
   (c) Erythema urticatum
   (d) Erythema bullosum

TABLE 3.—*Résumé of Cases*

Case	Age, Yr.	Entry	Prodomal Symptoms	Stomatitis	Conjunctivitis	Balanitis	Dermatitis	Days of Fever	Involvement of the Respiratory Tract	Bacteriologic Studies
1	27	10/13/41	Erosion of glans penis and dysuria	Patchy pseudomembrane	None	Erosion about meatus	None	3	None	No Vincent's organisms in the mouth
2	22	1/19/42	Cold and cough	Patchy pseudomembrane	Catarrhal	....	....	9	Bronchopneumonia of the lower lobe of the right lung	A few Vincent's organisms in the mouth
3	26	2/15/42	Cold and cough	Vesicles, then patchy pseudomembrane	Mucopurulent	None	Iris lesions on palms, soles and forearms	6	Dry cough	Not done
4	27	2/26/42	Cold	Patchy pseudomembrane	None	None	None	1	None	Not done
5	21	3/ 4/42	Photophobia, cold and cough	Vesicles, then patchy pseudomembrane	Purulent	Vesicles, then pseudomembrane	None	7	Productive cough	Not done
6	22	3/12/42	Cold and fever	Vesicles, then patchy pseudomembrane	Mucopurulent	None	None	4	None	Vincent's organisms present in the mouth
7	21	3/19/42	Cold and cough	Vesicles, then patchy pseudomembrane	Catarrhal	None	None	0	None	No record
8	27	4/24/42	Cold, cough and photophobia	Patchy pseudomembrane	Catarrhal	Pseudomembrane	None	0	None	Not done
9	25	5/11/42	Cold, cough, fever and malaise	Vesicles, then confluent pseudomembrane	Mucopurulent	Erosion and maceration of glans	None	12	Productive cough; rhonchi in chest	Staphylococci and streptococci in the mouth, no Vincent's organisms; hemolytic Staph. aureus in eyes
10	24	5/24/42	Cold, cough, fever and photophobia	Confluent pseudomembrane	Catarrhal	Erosion about meatus	None	7	Productive cough	Not done
11	28	6/ 4/42	Cough, sore throat, fever and headache	Vesicles, then patchy pseudomembrane	Catarrhal	Pseudomembrane	None	10	None	Not done
12	24	6/ 8/42	Cold and cough	Vesicles, then patchy pseudomembrane	Mucopurulent	Pseudomembrane	Maculopapules on forearms	9	Productive cough	No record
13	24	1/ 2/43	Cold and cough	Vesicles, then patchy pseudomembrane	None	Erosion about meatus	None	0	None	Not done
14	21	1/ 3/43	Cold, cough and sore throat	Vesicles, then patchy pseudomembrane	None	None	None	1	None	Not done
15	30	2/24/44	Cold and cough	Vesicles, then patchy pseudomembrane	None	Erosion and maceration of glans	None	0	None	Not done
16	31	2/14/44	Sore throat, cold and cough	Vesicles, then patchy pseudomembrane	Purulent	Erosion, maceration, and secondary infection	None	8	None	Hemolytic Staph. aureus in the eyes
17	18	4/ 2/44	Cough and fever	Patchy pseudomembrane	Catarrhal	Pseudomembrane	Iris lesion on palms and soles	9	Productive cough; rales in the lower lobes of both lungs	Streptococci and Staph. aureus in the mouth; no Vincent's organisms
18	24	10/13/44	Cough, cold and fever	Vesicles, then patchy pseudomembrane	Catarrhal	None	None	7	Productive cough; patchy pneumonia in the lower lobe of the right lung	Alpha streptococci and nonhemolytic Staph. aureus in the mouth; no Vincent's organisms
19	24	1/18/45	Cold, cough, aches, malaise and fever	Vesicles and bullae; later diffuse pseudomembrane present	Severe purulent; some pseudomembrane present	Bullae; later pseudomembrane formed also on prepuce and scrotum	Iris lesion on extensor surfaces of arms and legs	16	Severe bronchitis with asthma; 500 cc. of sputum daily	Mixed organisms in mouth, eyes and genitals; no Vincent's organisms
20	18	1/30/45	Cough for 3 wk.; burning eyes and blisters in mouth	Patchy pseudomembrane	None on entry; gave history of sore eyes	Slight erosion of meatus	None	1	Slightly productive cough; few coarse rales in base of right lung	No Vincent's organisms in mouth

marily; the type called ectodermosis pluriorificialis erosiva, and, finally, the Stevens-Johnson type. His cases fall into the second group, as do most of those described in this article, the condition being less severe than the Stevens-Johnson type in that the ocular manifestations do not progress beyond purulent conjunctivitis and the cutaneous lesions are usually limited to the extremities and are vesicular rather than hemorrhagic or maculopapular (table 2).

PRESENTATION OF A CASE

Table 3 presents a résumé of the cases in this series. A typical case is presented here.

CASE 19.—E. R., aged 24, entered the hospital on Jan. 18, 1945, with a history of backache for two months and headache, cough and fever for two days. In addition, he had noted nausea and vomiting for the previous two days. There was no relevant past history. The only medicament taken had been a prophylactic dose of 2 Gm. of sulfadiazine three months before.

On initial examination the only findings indicative of the disease were moderate conjunctival injection and an oral temperature of 102 F.

Course.—During the next week the temperature reached 102 F. daily. Medication included acetylsalicylic acid, acetophenetidin, caffeine and codeine. Nothing new developed until January 24, when many vesicles appeared in the mouth, some hemorrhagic. During the next several days the patient became toxic and the daily temperature rose to 104 F. Cough increased and became productive of much thick, mucopurulent sputum. The patient complained of substernal distress, and sibilant rales and expiratory rhonchi developed throughout both fields of the lungs. New vesicles and bullae, up to 1.5 cm. in diameter, appeared in the mouth until January 28 and then ruptured and gave way to a diffuse pseudomembrane which covered the lips, buccal mucosa, under surface of the tongue, palate and pharynx. Patchy membrane was present on the gums, which, however, did not show swelling, erythema, retraction or marginal ulceration at any time. The voice sank to a whisper, but laryngoscopic examination could not be tolerated. Compression of the larynx elicited pain. Swallowing became impossible, and for one week the patient was maintained on fluids administered intravenously, plasma and two blood transfusions. Some relief from soreness of the mouth was obtained by the use of sprays of tetracaine hydrochloride and irrigations with potassium permanganate.

Coincident with the onset of the stomatitis the conjunctivas became inflamed and drained purulent material. By February 29 a thin gray pseudomembrane appeared at the base of both lower tarsal sacs. At the same time small patches of pseudomembrane were evident on the turbinates of the nose bilaterally. Previously there had been nasal injection, crusting and occasional nosebleeds.

The skin finally became involved on February 27, when scattered erythematous macules averaging 1 cm. in diameter appeared on the extensor surfaces of the knees and elbows. These gradually became papular, and eventually developed either a central vesicle or a central area of clearing. A few new lesions made their appearance in the next several days, also involving the extensor surfaces of the ankles, thighs and upper parts of the arms. These persisted for seven to ten days, then crusted and finally left brown areas of pigmentation. Changes on the penis began at the same time, with injection and maceration of the glans followed by formation of bullae and, eventually, pseudomembrane. Interestingly, spread due to contact occurred on the prepuce and adjacent scrotum.

The patient continued to have a remittent temperature up to 104 F., which gradually subsided by March 2. Bronchial involvement was striking, at times 500 cc. of mucopurulent sputum being produced daily. Because of the large amount of sediment in the sputum, it was suspected that considerable desquamation was occurring in the bronchial mucosa. By February 30 there was noticeable general improvement. The patient took 1,300 cc. of bland fluids by mouth. By February 2 some peeling of the oral membrane had occurred and the tarsal membrane was gone. By February 5 the eyes and nose were clear, the cough was minimal and a soft diet was being taken. In the next ten days oral and penile pseudomembranes gradually disappeared. The tongue had desquamated completely, leaving a red, smooth dorsal surface.

A total of 500,000 units of penicillin was given intravenously from February 24 to February 29, without apparent effect. Penicillin ointment was used on the penis and in the eyes.

Laboratory Data.—The white blood cell count averaged 10,000 per cubic millimeter, but on one occasion it reached 15,000, with a fairly normal differential count. The urine was normal at all times. The mouth contained no Vincent's organisms. Smears and cultures revealed a variety of organisms, including staphylococci and diphtheroid organisms. From the eye were cultured Staphylococcus aureus and two strains of diphtheroid bacilli. From the sputum were obtained Staph. aureus, Streptococcus viridans, Neisseria catarrhalis and Hemophilus, influenzae. Decided phagocytosis of H. influenzae and gram-positive cocci were noted for several days. On the penis there were diphtheroid bacilli and Staph. aureus. Culture of the blood was sterile.

COMMENT ON CASES

Discussion here will be limited to a few pertinent features illustrated by the histories of the cases in this series (table 4).

None of the patients presented serious ophthalmologic problems. Their illnesses were milder in general, although in cases 9 and 19 the condition was as severe as many of those reported elsewhere. In 2 patients stomatitis was the only finding. One man was admitted to a ward for patients with conditions within the genitourinary tract because of dysuria and penile lesions, which were his initial complaints. Oral symptoms did not appear until three days later. Regarding seasonal incidence, table 1 indicates that in 90 per cent of the cases the condition occurred from January to June inclusive, as originally reported by Hebra and confirmed by others. The age incidence ranged from 18 to 31 years, considerably higher than in any previous experience, demonstrating that this is not a pediatric problem exclusively but one which concerns the internist as well.

In the search for causative factors, ingestion of drugs was considered. In 3 instances acetylsalicylic acid was taken during the prodromal period, and in 2 codeine was taken. Nothing in the past histories of the patients indicated any idiosyncrasy to these substances. Phenolphthalein was considered, but no one admitted taking it in any form and it was not available in the local medical supply. Several had received 2 Gm. of
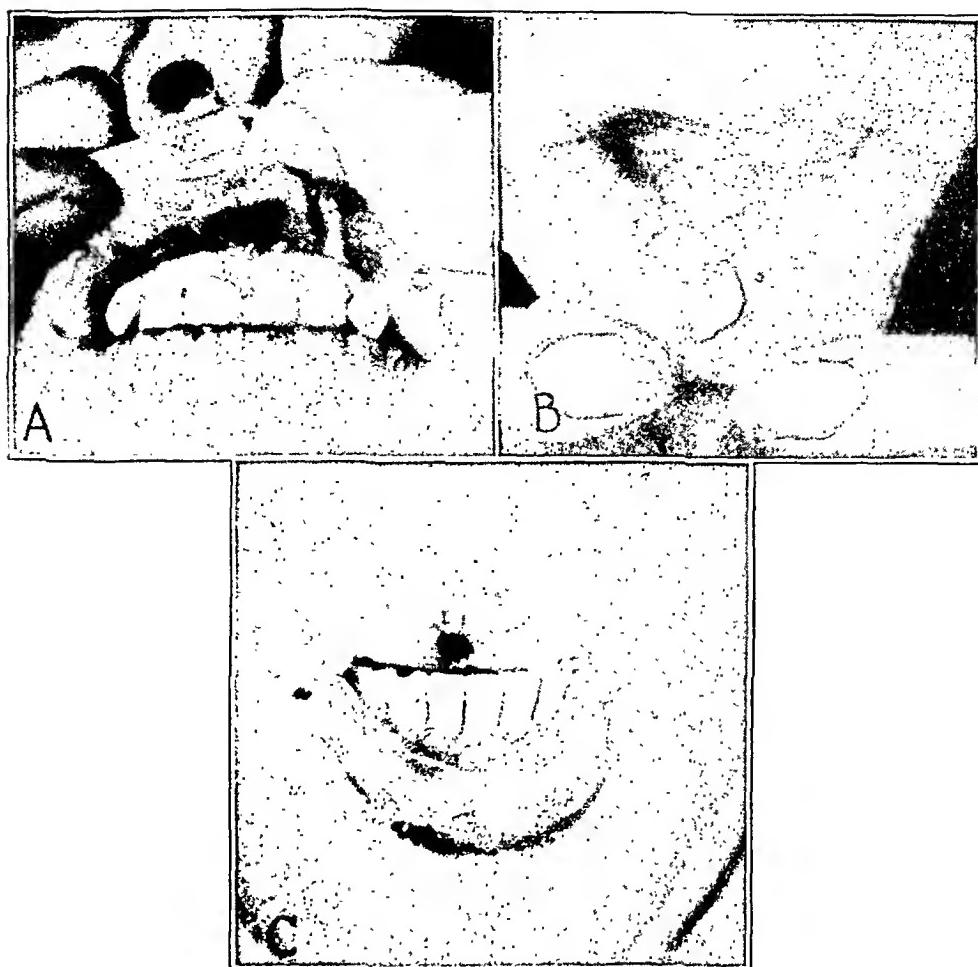
Fig. 2.—*A* and *B*, late pseudomembrane on the buccal surfaces. *C*, late pseudomembrane on the lips.

Fig. 3.—Erosion, maceration and pseudomembranous involvement of the penis.

sulfadiazine three to four months before. Two had sulfonamide therapy during the course of the disease. The men were all well nourished and healthy and had had at least several months of adequate diet in the service.

TABLE 4.—*Incidence of Symtoms and Findings*

	Literature	Present Series
Total number of cases	22	20
Prodromal respiratory symptoms		
Present	10	19
Absent	?	1
Fever and duration		
Afebrile	?	4
1 week	3	9
2 weeks	4	6
3 weeks	5	1
4 weeks and more	3	0
Not recorded	7	..
Cutaneous lesions		
Vesicular or bullous	13	3
Maculopapular	7	1
None	2	16
Oral involvement		
Vesicular	6	13
Vesicular with ulceration	4	0
Pseudomembranous	7	7
"Stomatitis"	2	0
None	3	0
Ocular involvement		
Conjunctivitis		
Catarrhal	0	7
Purulent	7	5
Pseudomembranous	3	2
Severe complications from corneal ulceration to		
panophthalmitis	10	0
None	2	6
Pulmonary involvement		
Bronchitis	4	7
Pneumonia	3	2
None	15	11
Genital involvement		
Balanitis	5	13
Urethral discharge	1	0
Vaginitis	1	0
None	15	7
Adenopathy		
Cervical	3	0
Generalized	1	0
None	18	20
Recurrent attacks	3	2
White blood cell count		
Leukocytosis	6	10
Leukopenia	1	0
Normal	5	5
Not recorded	10	5

Symptoms in the respiratory tract initiated the illness in 19 out of 20 cases as contrasted with 10 of the 22 cases in the literature. These varied from a cold in the milder instances to dry or productive cough, sore throat and generalized malaise in the more severely ill patients. Only 1 patient complained of the rheumatic pains that have been men-

tioned occasionally in the literature. The foregoing symptoms usually were of short duration. Three patients were admitted to wards for patients with conditions within the respiratory tract. Findings were minimal and limited to nasal congestion and discharge, slight redness of the throat and some tarsal conjunctival injection. One patient improved and was discharged after three days, and then acute soreness of the mouth, with vesiculation, developed several hours later. In the other 2 oral symptoms and signs developed on the second and third days respectively in the hospital. All other patients entered the hospital with lesions on the mucous membrane well established. In 7 cases bronchitis persisted, as manifested by cough productive of mucoid to purulent sputum and coarse rales and rhonchi usually in the bases of the lungs. In 1 unusual case 500 cc. of viscid, mucopurulent, blood-tinged sputum was collected in one day. In addition, moderate broncho-spasm was present for several days. In 2 other patients patchy broncho-pneumonia developed in the lower lobe of the right lung. Fever occurred in 16 cases and was of an irregular type, the temperature reaching 104 F. and lasting sixteen days in 1 patient.

Conjunctivitis, encountered in 14 cases, was usually present from the onset and involved, in the main, the tarsal portion. The membrane became reddened and velvety, and in 5 patients a mucoid to purulent discharge ensued. Appearing as a late manifestation, a linear, fairly adherent, paper-thin, gray-white pseudomembrane was found at the base of the lower tarsal sacs in 2 patients.

A few salient features of the oral manifestations deserve emphasis. These early observations were constant in this series, while absent in 3 of the cases in the literature. Sites of predilection in decreasing order of frequency were the inner aspects of the cheeks and lips, palate, under surface of the tongue, vermilion border of the lips, fauces and, lastly, superior aspect of the tongue. Redness was never an initial symptom, and swelling or edema was never present. Vesicles would appear rapidly and run their course to rupture in twenty-four hours. They were usually round to oval, transparent and extremely superficial and averaged 5 mm. in diameter, although at times bullae up to 2 cm. in greatest diameter replaced them. Within forty-eight hours the ragged and wrinkled external shells plastered down to form gray-white membrane which became secondarily infected, dull, covered with viscid slime and fetid in odor. In the severe conditions, in which a confluent membrane extended from lips to fauces, pseudomembrane appeared, without prior vesiculation, to fill the spaces between ruptured and intact vesicles. Salivation became progressively more notable. Extreme discomfort, total inability to swallow, great pain on opening the mouth or protruding the tongue, cracking and bleeding of the lips and secondary formation

of crust were striking. Examination of the posterior part of the pharynx proved impossible in these cases. Unfortunately laryngeal examination was not done in the healing stage. Aphonia and laryngeal tenderness indicated local involvement in 1 patient. Recovery began within nine to fourteen days. The pseudomembrane became clean and glistening, and oval red patches of new mucous membrane appeared after desquamation. Soreness decreased, and swallowing became easier. Within a week or two the membrane progressively peeled off, erythema disappeared and finally the last patches disappeared from the areas opposing the teeth.

The genital manifestations were interesting in that they paralleled those of the mouth in character. They usually appeared several days after the oral lesions. Genital involvement was noted in 13, or 65 per cent, of the patients as contrasted to only 6, or 28 per cent, in the literature. Reported incidence of these manifestations was increased by alertness for their presence and repeated examination for them. Frequently, only light redness and stickiness were noted about the meatus, with initial dysuria. Inflammation spread locally. Vesicles and pseudomembrane covered the glands in a patchy or confluent manner in the severer conditions. In 1 patient what seemed to be a spread due to contact occurred on the free margin of the redundant foreskin in ring fashion. From here, areas of maceration and oozing appeared on the anterior portion of the scrotum. Usually, however, the process was confined to the glans.

Iris lesions were the only dermal manifestation. These were scattered over the extremities and usually appeared in the second to third week of illness.

Perianal or intestinal involvement was not seen. In 1 patient small patches of pseudomembrane were present on the nasal septum for several days.

With as extensive an inflammatory process as occurred in the mouths of some patients, it is at first rather surprising that cervical adenopathy was not found at all in this series. This may be explained by the confinement of the process to the epithelial barrier as contrasted to herpetic stomatitis, in which ulceration leads to the consistent finding of regional adenopathy.

Bacteriologic examination of the various exudates and secretions revealed the usual mixed flora indigenous to the respective areas. The urine was normal in all the patients. In 10 leukocytosis was found, ranging from 12,000 to 24,000 cells, and in none was there leukopenia. Stevens and Johnson, because of 1 case, suggested the latter finding as a prerequisite feature for diagnosis, but this was later refuted by Ginandes. Results of a biopsy of skin taken from the patient in case 19 are

reproduced elsewhere and illustrate the changes described by McCarthy.[26] Common values in blood chemistry were checked in some of the patients. No significant alterations were noted except in the chloride metabolism, conservation of the chloride content of the body being observed. Of 12 patients, 3 were found with initial blood values below 400 mg. per hundred cubic centimeters, namely 366, 360 and 380. Total chloride content in the urine dropped from a normal of 5 to 15 Gm. in a twenty-four hour period to less than 1 Gm. Some chloride was lost in the saliva, values up to 2.6 Gm. in twenty-four hours having been reached. The contraction in the chloride economy is undoubtedly largely due to decreased intake because of dysphagia and loss through perspiration.

PATHOLOGY

The best description of the microscopic changes in the skin in erythema exudativum multiforme has been given by McCarthy. Essentially, there is an acute inflammatory process in the epidermis, characterized by edema, congestion and hemorrhage followed by round cell infiltration and, finally, exudation of fluid splitting the cell layers to form vesicles, bullae and sloughs. Bullous lesions here are identical clinically and histologically with those of pemphigus, and the two can be differentiated only by their clinical courses. McCarthy concluded that "we are dealing with a generalized infectious process producing a toxin that is circulated in the blood stream. The histological findings bear this out, and we cannot agree with the view that this is a primary disease of the epithelium."

No deaths have been reported in the literature in the English language except for Smith's questionable instance. Dr. Carl Weller was unable to make a specific diagnosis at autopsy in this case but suggested that because of the apparently spontaneous nature of the eruption of the skin and mucous membrane the condition might be in the class of epidermolysis bullosa. Microscopic examination revealed congestion and edema of the brain, spinal cord, bronchial nodes, thymus, spleen, pancreas, liver and kidneys. Various stages of inflammation, with formation of pseudomembrane, were present in the larger bronchi, tongue, pharynx, larynx and esophagus. The skin showed bullous lesions, with desquamation and superficial ulceration. The changes were sharply limited to the epidermis and upper part of the corium. Bilateral severe purulent bronchitis and bronchopneumonia were present. A streptococcus of unspecified type was found in the upper respiratory tract and esophagus and was considered to be possibly a secondary invader.

The European literature, cited by Blair, includes fatal cases reported by Hebra, Grigorow, Leloir, Hanke[27] and others. No mention can

26. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931.

27. Hanke, V.: Der Herpes iris des Auges, Arch. f. Ophth. **52**:263-284, 1901.

be found of results of histologic studies of the oral lesions, but, from the clinical similarity in onset and progression to those of the skin, the .process is presumably similar. That similar lesions of the larynx, esophagus and rectum can occur has been mentioned by Blair and also by Butler. No reports of microscopic studies of the ocular manifestations were found.

Thus, in summary, there are no distinctive pathologic changes found in erythema exudativum multiforme. Histologic changes in the skin are fairly typical but not specific. Visceral involvement is varied and inconstant, ranging from diffuse inflammatory to pseudomembranous change.

PATHOGENESIS

Investigation of etiology has been haphazard and much neglected. Bacteriologic studies have revealed nothing significant. The cutaneous lesions are usually sterile or contaminated by the staphylococcus. Smears and cultures of material from the mouth and pharynx usually reveal a mixture of flora but a surprising absence of Vincent's saprophytes. Pyogenic organisms are frequently found in the conjunctival discharge and, in a secondary role, probably account for much of the more serious ocular complications. Cultures of the blood are disappointing.

Several investigators have tried inoculation of animals, without significant result. Givner and Ageloff attempted culture of vesicle fluid in yolk sacs. Edgar and Syverton injected similar fluid into guinea pigs, rabbits and mice by all routes. After intravenous administration, 2 rabbits died in anaphylactic shock. Transfer from these animals to others was unsuccessful.

None of the patients who were specifically questioned gave any history of prior ingestion of drugs.

EXPERIMENTAL WORK

With the helpful cooperation of Capt. Alfred C. Florman, Medical Corps, Army of the United States, and the Ninth Service Command Laboratory, attempts were made to establish viral causation. Ideally, isolation of the virus from fluid in the vesicles should be attempted. However, the oral vesicles are so transitory that this did not prove feasible. After much fruitless waiting, it was decided that saliva taken from the patient in case 19 at a time when many freshly ruptured vesicles were present in the mouth would be used for studies on inoculation. The experimental work is summarized here.

I. *Attempts at Isolation with Saliva from the Patient in Case 19.*—Work was started on Jan. 30, 1945, when the frozen, stored specimen of saliva was thawed, diluted 1 to 5 with 2 per cent rabbit serum and inoculated onto the corneas of 3 rabbits. No reaction occurred during eleven days of observation.

The remainder of the saliva was passed through a Mandler 6 filter, and a portion was inoculated intracerebrally on two occasions into each of two groups of 6 Swiss mice. These mice were followed for twenty-one days, but no apparent disease developed.

Some filtrate was also inoculated by the Burnet technic onto the chorio-allantoic membrane of ten to twelve day embryonated chick eggs. Three separate series, the original filtrate being used, were studied. The first time, five serial passages were carried out at three to four day intervals; the second time, three serial passages were done, and the third time, fifteen serial passages were completed. These involved 92, 27 and 163 eggs repectively. In each series a somewhat similar picture was produced on some of the membranes. However, despite the fifteen serial passages (each time the membranes with the most extensive lesions were passed) this reaction could not be reproduced with any degree of uniformity or predictability.

The lesions consisted of either a relatively large, thickened plaque, usually central and with a crater-like area of necrosis, or a number of small, pinpoint-sized, thickened areas. On microscopic examination these were found to represent varying degrees of ectodermal proliferation. The cells immediately adjacent to the craters or at the center of the smaller plaques were swollen and appeared to contain cytoplasmic vacuoles. In the underlying mesoderm there was some evidence of edema and an increase in eosinophils.

Unfortunately, this type of reaction is not specific. The lesions resemble, in some respects, the reactions produced by some of the viruses as well as those

TABLE 5.—*Result of Examination of Serum*

	Specific Date	Herpes Neutralization	Elementary Body Complement Fixation, Titer
Case 19	1/30/45	Protected against more than 100 MLD	10
	2/10/45	Protected against more than 100 MLD	10
L. A.*	2/24/45	Protected against more than 100 MLD	10
	5/28/45	Protected against more than 100 MLD	
H. U.*	4/16/45	Protected against 30 MLD	
R. U.*	2/24/45	Protected against more than 100 MLD	10

* Later patients, not seen by the author.

which may follow trauma or hemorrhage. In addition, their relationship to the patient's illness remains to be shown, since they could not be inhibited by a specimen of serum obtained during convalescence.

Attempts to identify the responsible agent were made, egg material from various passages being used. Baby and mature rabbits, albino guinea pigs and white rats were inoculated intracerebrally, intracutaneously and on the cornea. Syrian hamsters and cotton rats were inoculated intraperitoneally. In all, 44 mice, 13 rabbits, 2 guinea pigs, 2 white rats, 2 cotton rats and 2 Syrian hamsters were used. No recognizable disease was produced except that in 1 mature rabbit out of 4 whose corneas were scarified and inoculated with material from the second egg passage of the first series keratitis developed. This appeared on the third day and cleared by the sixth day. No encephalitic symptoms were reproduced with this inoculum, which had been stored in the frozen state, or with material from later passage.

In the absence of a more uniformly susceptible laboratory animal, further work on this aspect of the study was discontinued.

II. *Serologic Studies.*—Because of the clinical similarity to herpetic stomatitis, herpes neutralization tests in mice and complement fixation tests for elementary viruses of the body type with the use of a chick embryo antigen (an inactivated suspension of the elementary bodies of the virus of lymphogranuloma venereum) prepared by E. R. Squibb & Sons were carried out. No significant results were obtained. Serums from the persons listed in table 5 were examined.

On an earlier occasion, the following neutralization tests were carried out against serums from the patients in cases 16 and 17 (table 6).

Five mice were used with each mixture of virus dilution and serum. The numbers in table 6 indicate the day of death for each mouse. The virus used had a titer of 10^{-44} in rabbit serum for a minimum lethal dose for 50 per cent of the animals. The degree of protection in acute and convalescent phases is seen not to be significantly or constantly altered.

DIFFERENTIAL DIAGNOSIS

The diagnosis of erythema multiforme exudativum is relatively simple if the following features are kept in mind. The disease primarily involves squamous and modified squamous epithelium, producing inflammatory

TABLE 6.—*Herpes Neutralization Test*

Final Virus Dilution	Normal Rabbit Pool	Case 16		Case 17		Normal Human Pool
		Acute 2/19/44	Convalescent 3/3/44	Acute 4/2/44	Convalescent 4/19/44	
10^{-1}	2	7	12	13	9	..
	3	—	—	—	—	..
	4	—	—	—	—	..
	4	—	—	—	—	..
	5	—	—	—	—	..
10^{-2}	4	—	9	5	—	—
	4	—	—	9	—	—
	5	—	—	—	—	—
	5	—	—	—	—	—
	7	—	—	—	—	—
10^{-3}	5	—	—	—	2	—
	5	--	—	—	4	—
	6	—	—	—	—	—
	6	—	—	—	—	—
	—	—	—	—	—	—
10^{-4}	5	..	..	..	..	6
	6	..	..	..	..	—
	9	..	..	..	..	—
	12	..	..	..	..	—
	—	..	..	..	..	--
10^{-5}	7	..	..	..	..	3
	—	..	..	..	..	—
	—	..	..	..	..	—
	—	..	..	..	..	—
	—	..	..	..	..	—

changes resulting in erythema, followed by exudation of fluid and ending in vesicles, bullae and pseudomembranes with or without secondary infection. Secondly, the involvement of the skin is a form of erythema multiforme but nevertheless follows a definite pattern of circumscribed, bilaterally symmetric, maculopapular erythema progressing to formation of fluid and regressing through fine crusting to persistent violaceous or brownish pigmentation. The term "multiforme" is confusing and does not apply to the individual patient, whose lesions are uniform throughout. In the author's series the few with involvement of the skin had, with one exception, the herpes iris type, indistinguishable from patient to patient. Thirdly, the lesions on the mucous mem-

brane go through a similar cycle to that in lesions of the skin, although confusion may arise through initial late contact with the patient at a stage when only pseudomembranes are evident. In these instances the patient, on careful questioning, will reveal that his trouble began with "water blisters." A pitfall to avoid is in the description of superficial erosions in the oropharynx as ulcers. True ulcers did not occur in this series or in the majority of cases in the literature. The description of these lesions is often so sketchy that doubt is engendered as to the accuracy of observation when ulceration is reported. However, it is conceivable that in a rare severe condition ulceration from secondary causes may occur.

Hebra's original conception of eruptive fever has been enlarged and beclouded by the much larger group of toxic erythemas popularly called erythema multiforme. These cutaneous reactions are due to a variety of causes, mainly drugs (bromides, cinchophen, common antipyretics, barbiturates, salicylates, phenolphthalein and sulfonamide drugs), and, to a lesser extent, systemic diseases such as rheumatic fever and Libman-Sacks syndrome. The latter is easily eliminated from consideration, but the former is less easily separated from eruptive fever and tends to overlap. In such cases there is usually a history of ingestion of drugs. Erythema tends to become confluent and generalized and frequently remains macular. Urticarial and petechial elements may appear, associated with pruritus. Lesions are usually in the same stage, and there is an absence of prodromes in the respiratory tract. Papular, vesicular and bullous rashes are less frequent. In the severer conditions involvement of the mucous membrane may occur, but it is usually minor and not at all proportional to the extent of the systemic and dermal upset. When the mouth is involved, patchy erythema is the most frequent finding, with vesicles and pseudomembrane occasionally seen. In the eyes there is seldom more than a catarrhal conjunctivitis. Dardinski's [28] recent report of a fatality due to the use of sulfadiazine illustrates the difficulties of diagnosis: During treatment for pneumonia, a generalized sunburn-like erythema, deep conjunctival injection and redness of the oral membrane developed in a 17 year old girl. Several detachable pieces of white membrane later appeared in the posterior part of the pharynx. The course became septic, many large coalescing bullae appeared over the body and death occurred three days after the onset of the rash. The organs were normal at autopsy. Microscopic examination of the skin revealed splitting of the epidermal layers by fluid, congestion and round cell infiltration in the dermis. Similarly, phenolphthalein may cause difficulty by producing bullous and erosive lesions

28. Dardinski, V. J.: Erythema Multiforme Bullosum Following the Use of Sulfadiazine, Am. J. Clin. Path. **15**:28-29 (Jan.) 1945.

in the mouth and on the genitalia, associated with a rash, which occasionally may be erythema multiforme. However, the more characteristic lesion is a fixed maculopapule of polychromatic hue with ill defined borders.

Pemphigus has many similar features, with its bullous involvement of the skin and mucous membrane, but it is easily distinguished by its chronicity, older age incidence, positive Nikolsky sign and dirty, oozing cutaneous lesions.

A number of children with severe attacks of eruptive fever were sent to hospitals for patients with contagious disease, the diagnosis of hemorrhagic measles having been made, but the differentiation from this and other forms of exanthema should present no real problem.

Conjunctivitis, rhinitis and balanitis are present in the rarely observed instances of foot and mouth disease in human beings, along with vesicular lesions on the extremities and in the mouth. However, the mouth is dry and burning, changes are present about the nails of the hands and feet, a virus can be demonstrated readily by inoculation of a guinea pig and, finally, the disease is nonexistent in this country. A number of cases reported as such in the literature, without confirmation by the inoculation of guinea pigs, may have really been cases of eruptive fever, according to Klauder.

The question of vitamin deficiency is occasionally brought up when physicians who are unfamiliar with the syndrome under discussion view the oral lesions. There is no type of known disease due to vitamin deficiency which simulates eruptive fever.

Acute disease of the mucous membrane of the mouth constitutes one of the most confused fields of medical interest and the one most in need of clarification and classification along etiologic and pathologic lines. This need for enlightenment is particularly pertinent to this discussion because of the general tendency to attach the diagnosis of Vincent's infection to most instances of acute stomatitis or gingivostomatitis.

The frequency with which the saprophytic fusiform bacillus and the spirochete Borrelia vincenti are found in normal as well as diseased mouths cautions against the attachment of too much significance to their presence as primary pathogens. Their role relative to this discussion can be dismissed by pointing to a complete lack of experimental evidence as to their ability to attack healthy mucous membrane. Before enumeration of the oral lesions which may be confused with the stomatitis of eruptive fever, it is important to clarify nomenclature and place it on an etiologic rather than descriptive basis. In eruptive fever or in herpetic stomatitis the various terms infectious, catarrhal, aphthous, ulcerative, membranous and pseudomembranous have been used as diagnostic handles, and yet these merely represent various stages in the cycle of conversion of a vesicle into an ulcer. In as recent an authoritative text as

that of "Oral Diagnosis," by Thoma,[29] the descriptive method of classification is still used. The author lists the following types.

Infectious Stomatitis.—Infectious stomatitis is an acute process characterized by edema, swelling of the membrane, regional adenopathy and fever, due to micrococcus or beta streptococcus. (This is an obscure condition and seems not to occur in the present day.)

Ulcerative Stomatitis.—Ulcerative stomatitis occurs in infants and young children and often is due to mixed infection of staphylococci and streptococci. There are fever; reddened, swollen mucous membrane, with ulcers on buccal, gingival and lingual surfaces, and regional adenopathy. (This corresponds best to herpetic stomatitis, to be described later.)

Ulceromembranous Stomatitis.—Ulceromembranous stomatitis seems to differ from the foregoing disease only in that the process starts in the gingival crevices, where the interdental papillae become decidedly swollen, and then spreads over the entire mouth. (This is probably herpetic stomatitis again.)

Membranous Stomatitis.—In membranous stomatitis false membrane forms throughout the mouth and pharynx. It can be detached easily, leaving a raw, bleeding surface. (This corresponds to the late oral phase of eruptive fever.)

In the past ten years Youmans,[30] Perrin Long,[31] Burnett and Williams,[32] Black,[33] Dodd, Johnston and Buddingh [34] and Scott and Steigman [35] have separated a new clinical entity, herpetic stomatitis, from the wastebasket of forms of stomatitis described previously and proved its causation by the virus of herpes simplex. These authors described an acute gingivostomatitis in infants and a few adults, isolated the virus by inoculation into the corneas and brains of rabbits, proved its identity with the herpes virus by protection tests on animals and demonstrated

29. Thoma, K. H.: Oral Diagnosis, with Suggestions for Treatment, Philadelphia, W. B. Saunders Company, 1943.

30. Youmans, J. B.: Herpetic Fever with Stomatitis: Report and Discussion of a Case in Which the Virus Was Isolated, South. M. J. **25:**228-233 (March) 1932.

31. Long, P. H.: Herpetic Pharyngitis and Stomatitis: Report of Three Cases, J. Clin. Investigation **12:**1119-1125 (Nov.) 1933.

32. Burnett, F. M., and Williams, S. W.: Herpes Simplex: New Point of View, M. J. Australia **1:**637-642 (April 29) 1939.

33. Black, W. C.: Etiology of Acute Infectious Gingivostomatitis (Vincent's Stomatitis), J. Pediat. **20:**145-160 (Feb.) 1942.

34. Dodd, K.; Johnston, L. M. and Buddingh, G. J.: Herpetic Stomatitis, J. Pediat. **12:**95-102 (Jan.) 1938.

35. Scott, T. F. M.; Steigman, A. J., and Convey, J. H.: Acute Infectious Gingivostomatitis: Etiology, Epidemiology and Clinical Picture of Common Disorder Caused by Virus of Herpes Simplex, J. A. M. A. **117:**999-1005 (Sept. 20) 1941.

rising protective antibody titers in their patients. Black fulfilled the postulates of Koch by inoculating the isolated virus into the mucous membrane of infants and thereby reproducing the disease. The various authors agreed on the term infectious or herpetic gingivostomatitis for the condition as revealed in their cases but varied somewhat in the description of their clinical observations. Some disagreement is recorded as to the identity of aphthous stomatitis, catarrhal stomatitis and membranous stomatitis with Vincent's stomatitis, fusospirochetal gingivitis, trench mouth and ulceromembranous stomatitis. However, Scott and Steigman sensibly commented that thirty descriptive terms are used to classify the various stages of herpetic stomatitis. This is an acute systemic infection characterized by fever, irritability, soreness of mouth; red swollen gums, oral fetor and regional lymphadenopathy. The primary finding is a tiny vesicle, which ruptures, leaving a shallow, round ulcer (aphthous ulcer) sometimes covered by a membrane. It may merge with adjacent ulcers. These lesions are most frequently found on the buccal and lingual surfaces but may also be present on the gums or anywhere else in the mouth or pharynx. The gums usually become red and swollen and bleed easily, and marginal ulcerations may develop. In a small percentage of the cases herpes simplex precedes or is associated with the oral changes. The disease is acute and self limited, and it usually runs its course in six to sixteen days. The various authors, in passing, relegated the fusospirochetes to the ash can of etiologic oblivion, where they probably belong. Scott and Steigman pointed out that trench mouth or Vincent's stomatitis in adults is due for an urgently needed reinvestigation in the light of the aforementioned observations.

A few instances of the disease in adults have been reported by Youmans and by Long. The latter isolated the herpes virus in 2 out of his 3 cases by repeated inoculation of animals. Thus the way has been paved to eliminate the term Vincent's disease entirely from any discussion of stomatitis.

Further to be differentiated is a new disease in infants and young children described by Buddingh and Dodd in 1944.[36] At the onset the mouth is sore and the mucous membrane of the lip, anterior margin and under surface of the tongue and the gums become fiery red and covered with tiny vesicles. These changes are followed by desquamation, leaving raw surfaces, which bleed easily. In older children with teeth, the involvement of the gums is severer, with swelling, vesicles and shallow ulceration. Many infants suffer from mild diarrhea. There is no fever, and the course is from three to ten days. Relapses may occur during the next two months. Contagion is striking, 16 instances having

36. Buddingh, J. G., and Dodd, K.: Stomatitis and Diarrhea of Infants Caused by Hitherto Unrecognized Virus, J. Pediat. 25:105 (Aug.) 1944.

occurred among 30 infants in a nursery within a period of two weeks. Swabs from infected mouths readily produced keratitis through multiple passages in rabbits, differing from the inclusion body type due to the herpes virus. This virus was also found in nurses and an intern who remained free from any symptoms. One of the authors accidentally flicked some infected corneal filtrate into his mouth, and on the third day typical oral lesions developed. Further work showed that humoral protective antibodies developed and that there were no cross relationships with the herpes virus, and the feeding experiments in rabbits produced shallow ulcerations in the small intestine.

TREATMENT

There is little that can be said on the subject of therapy. The local lesions cannot be significantly influenced. Nothing stronger than solution of boric acid was used in the eyes. Some of the earlier authors felt that vigorous measures were needed to prevent serious ocular complications. Perhaps because the disease was milder such was not the case here. In the mouth, irrigations with potassium permanganate in a 1 : 4,000 dilution were as effective as anything else in the maintenance of cleanliness. It is felt that the use of caustic agents such as silver nitrate has no place in the treatment of diffuse lesions. Local anesthetics such as tetracaine hydrochloride or ethyl aminobenzoate, best used in a jelly, are of some slight value in relieving the soreness. As far as systemic therapy is concerned, penicillin in large doses was tried in case 19, without appreciable effect. The sulfonamide drugs were avoided because of the eruptive manifestations and the absence of any good or urgent indication for their use. High vitamin therapy was ineffectual when tried.

SUMMARY

1. Twenty cases have been reported of an obscure and little-recognized syndrome in young men, constituting an acute, probably infectious, self limited, febrile disease. Prodromal symptoms in the respiratory tract are followed by lesions of the skin and mucous membrane of the mucocutaneous junctions, characterized by vesicles and pseudomembranes and accompanied frequently with fever and occasionally with bronchopneumonia.

2. Three groups are recognized, based on severity and distribution of lesions. The first group, originally described by Hebra as erythema multiforme exudativum, includes mild conditions primarily involving the skin, with only slight involvement of the mucous membrane. The second group, described by Stevens and Johnson, includes extremely severe conditions, with extensive lesions of the mucous membrane, corneal scarring, panophthalmitis and blindness. The third group, including conditions of intermediate severity, is exemplified by the cases in the series described here.

3. The pathogenesis is obscure. Bacteriologic findings are not of significance. There is no evidence that ingestion of drugs is a factor. Because of the prodromes in the respiratory tract and generalized manifestations, it is felt that this is an air-borne, systemic disease probably due to a virus.

4. Experimental studies failed to demonstrate a humoral antibody response to the herpes simplex or elementary virus of the body type. Various experiments in inoculation with filtered saliva from 1 patient were largely noncontributory, although some suggestive lesions were produced in chick embryos. It is believed that future investigation directed along these lines is indicated, with the consideration of the use of human volunteers.

5. In the foregoing paragraphs the terms erythema exudativum multiforme, eruptive fever and Stevens-Johnson disease have been used interchangeably in the description of the syndrome under discussion. The various names proposed and used are ponderous, frightening and misleading in that they direct attention almost exclusively to the skin. Erythema exudativum multiforme means little in the majority of cases in this series, in which dermatologic lesions did not occur. The term "erythema pluriorificialis exudativum" is better chosen in that it refers also to the orifices of the body, but it is still too long and cumbersome for common usage and has descriptive meaning only. Until the causative agent is found, appropriate naming of this disease will not be possible.

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CIRRHOSIS OF THE LIVER WITH MASSIVE HYDROTHORAX

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ALTHOUGH the first description of massive hydrothorax occurring in a case of cirrhosis of the liver has been attributed to Laennec, it has since received scant clinical attention. As a result, its development frequently transforms an otherwise obvious case of cirrhosis of the liver into a puzzling diagnostic problem. It has been cited by Vedel and Puech [1] as occurring in 8 to 9 per cent of all cases of cirrhosis of the liver. However, these authors arrived at this relatively high incidence by the inclusion of cirrhotic patients having tuberculous or cardiac pleural effusions. Few reports are available in which the complicating causes for hydrothorax have all been demonstrated to be absent.

Goffart [2] and Benedetti [3] each reported a small series of cases of cirrhosis with hydrothorax and attempted to exclude the more usual causes of hydrothorax. Christian [4] reported a case of hydrothorax on the left side requiring nine thoracenteses, with the withdrawal of a total of 13,100 cc. of fluid. An additional case of cirrhosis, in which the diagnosis was confirmed by biopsy, without any clinically demonstrable pathologic changes in the lungs, mediastinum, pleura or heart was reported by Frothingham.[5] The recurrent hydrothorax involving the right side necessitated two hundred and eleven thoracenteses for the removal of a total of 467,100 cc. of fluid from the right pleural cavity. In view of this paucity of reported cases, it seems reasonable to conclude that massive hydrothorax with no etiologic basis other than

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1. Vedel, S. N., and Puech, A.: Considerations sur les épanchements pleuraux au cours de la cirrhose de Laënnec, Bull. Soc. d. sc. méd. et biol. de Montpellier **8**:120, 1927.

2. Goffart, M.: Étude clinique et biologique des épanchements pleuraux des cirrhotiques, Rev. belge sc. méd. **10**:341, 1938.

3. Benedetti, P.: Ill grande idiotorace destro nel corso della cirrosi epatica, Arch. di pat. e clin. med. **20**:119, 1939.

4. Christian, H. A.: Bloody Pleural Fluid, an Unusual Complication of Cirrhosis of the Liver, Ann. Int. Med. **10**:1621, 1937.

5. Frothingham, J. R.: Cirrhosis of the Liver Complicated by Persistent Right Hydrothorax and Ascites, New England J. Med. **226**:679, 1942.

cirrhosis of the liver is rare. During the years 1930 to 1945 only 6 cases of this syndrome were seen at this laboratory. These cases were selected from approximately 600 cases of cirrhosis of the liver. We have observed, as have the older authors, that not infrequently small amounts of pleural effusion are found in cases of cirrhosis of the liver, but these are usually the result of associated pathologic conditions and not of the hepatic disease. For this reason we have established the following criteria for the selection of our cases: (1) the presence of an uninfected hydrothorax of more than 500 cc. possessing the characteristics of a transudate and (2) the presence of cirrhosis of the liver uncomplicated by any other disease which may produce hydrothorax.

Because of the high incidence of cardiorenal disease in this age group and because of the relationship of disease of the heart, lungs and kidneys to the accumulation of pleural fluid, a special effort was made to exclude patients having significant pathologic changes in these organs. To this end all patients with hearts weighing more than 350 Gm. or showing gross or microscopic evidence of organic cardiac disease were excluded. To exclude cardiac failure further, patients with lungs weighing more than 450 Gm. or showing gross or microscopic evidence of significant pulmonary edema were omitted from the series. In all cases the kidneys were within normal limits grossly and microscopically.

Of the 6 cases included in the present series, 2 have been selected for citation in detail.

CASE 1.—A 65 year old ship rigger entered the hospital complaining of progressive weakness and dyspnea of about three months' duration. He had lost 15 pounds (6.8 Kg.) during this period and had noted the onset of a cough producive of whitish sputum. His appetite had been poor for several months prior to his admission to the hospital. Until a year before admission he had consumed large quantities of alcoholic beverages. His previous health had been good except for an attack of typhoid fever in 1906.

The blood pressure was 125 systolic and 80 diastolic. He appeared acutely ill and was decidedly orthopneic. The skin of the face and upper part of the thorax was ruddy, and a number of telangiectases were present. No jaundice was noted. The trachea was deviated to the left, and the entire right side of the chest was flat to percussion, with absence of breath sounds and diminished fremitus. A smooth, nontender edge of liver was palpated at the level of the umbilicus.

The urine was normal except for the presence of bile. The hemoglobin content was 14 Gm. per hundred cubic centimeters. The white blood cell count was 9,650. The prothrombin time was 55 per cent of normal. The total serum protein content varied between 5.93 and 6.99 Gm. per hundred cubic centimeters. The nonprotein nitrogen content was 27 mg. per hundred cubic centimeters. The acid phosphatase content was 1.32 units per hundred cubic centimeters and the alkaline phosphatase level 1.51 units. The cephalin flocculation test gave a reaction of 3 plus, and the hippuric acid excretion was 0.88 Gm. Inoculation of gastric washings into a guinea pig showed them to be negative for tuberculosis.

From 1,000 to 4,000 cc. of clear yellow to cloudy fluid was removed from the right pleural cavity on numerous occasions at intervals varying from three days to three weeks. The specific gravity of this fluid varied between 1.013 and 1.016. Culture and inoculations of a guinea pig with it showed it to be sterile. Repeated histologic sections of the sediment were reported negative for tumor cells except for one specimen reported as "suggestive of carcinoma."

Roentgenograms of the chest showed a massive accumulation of fluid on the right, with atelectasis and displacement of the mediastinum to the left. A series of roentgenograms of the gastrointestinal tract and a series of the bony skeleton were noncontributory. The electrocardiogram was within normal limits. Peritoneoscopy did not demonstrate conclusively the presence of cirrhosis, because of poor visualization of the liver. Bronchoscopy revealed only tracheobronchial displacement, with mucosal scarring suggestive of healed tuberculosis.

The patient remained in the ward for four months while these diagnostic studies were performed. He required repeated thoracentesis because of the rapid reaccumulation of the fluid in the right pleural cavity. He became progressively weaker, was disoriented during the last two weeks of his stay in the hospital and died in a stuporous condition. The diagnosis on discharge was bronchiogenic carcinoma with metastases to the pleura, recurrent massive hydrothorax on the right side, alcoholic cirrhosis of the liver and malnutrition.

An autopsy was performed thirty-two hours after death. Only the pertinent findings are given.

The peritoneal cavity contained approximately 500 cc. of clear, straw-colored fluid. The right pleura was thickened to 0.4 cm. The right pleural cavity contained 3,000 cc. of clear, yellow fluid. Several bandlike adhesions bound the apex of the collapsed right lung to the thoracic wall. The left pleural cavity was moist but contained no free fluid. The mediastinum was deviated to the left. The pericardial cavity contained an estimated 50 cc. of straw-colored fluid. Grossly, the diaphragm was intact.

The right lung weighed 220 Gm. and the left 420 Gm. The right lung was small, collapsed and covered by a thick layer of stringy yellow fibrin. The cut surface was firm, red and meaty. The left lung appeared slightly congested, and a foamy fluid emerged from the bronchioles on compression of the lung. The vessels, trachea and bronchi were not remarkable. The hilar and mediastinal lymph nodes were not enlarged.

The liver weighed 910 Gm. The capsular surface was tawny and finely nodular, the nodules measuring 0.1 to 0.3 cm. in diameter. At the anterior margin of the left lobe was a depresseed, soft, red area, 2 cm. in diameter, which extended into the hepatic substance for a distance of 1 cm. The liver was firm and resistant to section, and the cut surface showed thin, gray septums dividing it into nodules similar to those seen on the surface. The heart, kidneys and brain were grossly within normal limits.

Microscopic examination of the various tissues substantiated the anatomic findings. The pleura of the right lung was thickened, vascularized and covered by a layer of fibrin. The alveoli were decidedly compressed and contained no inflammatory reaction. The left lung showed only moderate congestion of the blood vessels. The lobular architecture of the liver was destroyed by broad bands of fibrous tissue, for the most part portal in distribution but occasionally bisecting lobules. The connective tissue contained numerous small bile ducts, lymphocytes, an occasional polymorphonuclear leukocyte and scattered small nests of hepatic cells. The normal central relationship of the veins was lost. Scattered focal areas of bile stasis were present. Only a few hepatic cells were vacuolated,

and alcoholic hyalin could not be demonstrated. A section taken from the anterior edge of the left lobe of the liver showed a partially fibrosed cavernous hemangioma.

The anatomic diagnosis was cirrhosis of the liver, unclassified type, with ascites, massive hydrothorax involving the right side and atelectasis of the right lung.

Comment.—The clinical course in this case was dominated by a massive hydrothorax which rapidly reaccumulated after thoracentesis. The cause of this hydrothorax remained undetermined in spite of diagnostic studies. A diagnosis of cirrhosis of the liver was established, but no relationship between the two conditions was considered. At necropsy cirrhosis of the liver, unclassified type, with massive hydrothorax on the right side and atelectasis of the right lung, was found.

CASE 2.—A 24 year old woman entered the hospital for the first time, complaining of pleuritic pain on the right side of eleven days' duration. The right side of her chest had been strapped by her local physician. Three months previously she had given birth to a living child, her pregnancy being complicated by toxemia in the eighth month. No jaundice, loss of weight or loss of appetite had been noted at any time.

The temperature was 96.6 F., the pulse rate 71 and the respiratory rate 20. The blood pressure was 98 systolic and 78 diastolic. There was limited motion of the right side of the chest, with decreased resonance to percussion and suppression of the breath sounds. A soft blowing apical systolic murmur was heard.

An uncatheterized specimen of urine contained albumin (4 plus) and was loaded with red cells. The hemoglobin content was 11 Gm. per hundred cubic centimeters. The white blood cell count was 7,650. The serum nonprotein nitrogen content was 29 mg. per hundred cubic centimeters. A phenolsulfonphthalein test resulted in the excretion of 100 per cent of the dye in one hour. The Aschheim-Zondek test elicited a negative reaction. The reaction to a tuberculin patch test was strongly positive. Culture of the pleural fluid was sterile, and on inoculations of a guinea pig samples of pleural fluid, gastric washings and sputum were shown to be negative for tuberculosis.

A thoracentesis was performed, and 800 cc. of clear yellow fluid was withdrawn from the right pleural cavity. After ten days in the ward the patient was discharged for rest in bed at home to await the reports on the inoculation of a guinea pig. The diagnosis on discharge was pleurisy with effusion and questionable tuberculosis.

Second Admission (Ten Weeks Later).—Six weeks after the patient's discharge a second thoracentesis had been performed and 1,000 cc. of clear, yellow fluid had been withdrawn from the right pleural cavity. Two weeks later the patient noticed that toward the end of the day her feet were swollen. A week later an itching eruption over the lower part of the legs appeared, and this spread to the thighs, abdomen and upper arms. On the day before her admission she experienced a pain in the right infraclavicular region, which was aggravated by coughing or deep breathing and partially relieved by lying on the right side.

Physical examination at this time showed an erythematous, punctate, partially confluent, scaling rash over the skin of the tibial regions, abdomen and upper part of the arms. The trachea was deviated to the left, and there was limited motion of the right side of the thorax, with flatness and absence of breath sounds up to the level of the scapular angle. The heart was displaced to the left. The abdomen was protuberant, with shifting dulness and a fluid wave. The liver and

spleen were palpable 2 fingerbreadths below the costal margins. Mild edema of the legs and thighs was noted.

The total protein content was 4.51 Gm. per hundred cubic centimeters. The cephalin flocculation test gave a reaction of 4 plus and the prothrombin time was 35 per cent of normal. A hippuric acid test showed the excretion of 0.3 Gm. in one hour. The urine revealed bile (1 to 2 plus) occasionally, and the stool was light tan to brown and reacted negatively to the guaiac test.

On thoracentesis a straw-colored fluid with a specific gravity of 1.004, 749 red cells and 18 white cells per cubic millimeter was withdrawn. A histologic section of the sediment was reported as showing "atypical cells suggestive of but not typical of carcinoma." Cultures of the fluid and repeated cultures of the blood were sterile.

Roentgenologic examination of the chest on three occasions disclosed large amounts of fluid in the right pleural cavity. An electrocardiogram was interpreted as suggestive of myocardial involvement.

During the ensuing six weeks the patient gave increasing evidence of severe hepatic failure, with the development of massive ascites and edema, jaundice, low grade fever, lethargy and finally coma. A total of 5,785 cc. of fluid was obtained on three thoracenteses, and one abdominal paracentesis yielded 2,600 cc. of fluid during the six weeks' course. She was placed on a high vitamin, high protein, high carbohydrate and low fat diet. Her rapid downhill course persisted, and she died in spite of supportive therapy six weeks after her final admission and sixteen weeks after her initial entry to the hospital.

The diagnosis on discharge was hepatic failure, subacute yellow atrophy (?), cirrhosis of the liver with superimposed hepatoma (?), lupus erythematosis (?) and Hodgkin's disease (?).

An autopsy was performed eighteen hours after death. Only the pertinent findings are discussed.

The peritoneal cavity contained about 700 cc. of blood-tinged fluid. The right pleural space contained 2,500 cc. of clear straw-colored fluid, and the right lung was decidedly collapsed. Several thin, weblike adhesions were present posteriorly. The left pleural cavity contained about 800 cc. of similar straw-colored fluid. The pericardial cavity contained approximately 60 cc. of clear fluid. The diaphragm was intact grossly.

The right lung weighed 300 Gm. and the left 420 Gm. The right lung was small, firm and gray. The cut surface was gray and dry. The left lung showed a moist, red, subcrepitant surface on cut section.

The liver weighed 1,020 Gm. The surface was irregularly nodular and had a dull yellow color. The liver sectioned easily and was flabby, and the cut surface showed a similar yellow nodularity with intervening gray strands of fibrous tissue. Small, red areas of softening were scattered over the cut surface.

The heart, kidneys and brain revealed no abnormalities. Microscopic examination of sections from the various organs substantiated the gross anatomic findings.

The lungs showed congestion of the vessels and collapse of the alveoli. No inflammatory exudate was present. The liver showed widespread destruction of hepatic cells, with collapse of the stroma and replacement by loose connective tissue containing large numbers of small bile ducts and congested sinusoids. In several areas the remaining hepatic cells appeared necrotic and were surrounded by polymorphonuclear leukocytes and vacuolated phagocytes. Several large nodules of regenerating hepatic cells surrounded by a band of compressed fibrous tissue were observed.

The anatomic diagnoses were healed acute yellow atrophy with superimposed acute yellow atrophy, ascites, bilateral hydrothorax, atelectasis of the right lung and pulmonary congestion.

Comment.—The initial finding in this case of a recurrent hydrothorax attributed to tuberculosis was followed ten weeks later by signs suggestive of hepatic failure. Although a relationship between the hydrothorax and the hepatic disease was considered, this diagnosis was not accepted. As a result, no definite diagnosis was established clinically. At autopsy an acute yellow atrophy superimposed on a healed acute yellow atrophy with bilateral hydrothorax and ascites was found.

Summary of Six Cases of Cirrhosis of the Liver with Massive Hydrothorax

Case; Sex; Age, Yr.	Amount (Cc.) and Character of the Pleural Fluid		Duration of Hydrothorax	Ascites (Cc.) (Amount and Character of the Fluid)	Anatomic Type of Cirrhosis	Clinical Diagnosis
	Right Side	Left Side				
1 M 65	3,000, clear yellow	0	6 mo.	500, clear yellow	Unclassified	Bronchiogenic carcinoma with pleural metastases and massive recurrent hydrothorax on the right and alcoholic cirrhosis
2 F 24	2,500, straw colored	800, straw colored	3½ mo.	700, blood tinged	Healed acute yellow atrophy with superimposed acute yellow atrophy	Right pleural effusion; tuberculosis (?); hepatic failure; subacute yellow atrophy (?); cirrhosis with hepatoma (?); lupus erythematosus (?); Hodgkin's disease
3 M 60	2,000, straw colored and fibrinous	1,000, straw colored and fibrinous	6 mo.	1,000, straw colored	Alcoholic	Alcoholic cirrhosis with bleeding; esophageal varices
4 M 42	1,000, bile tinged	200, bile tinged	1 mo.	4,700, bile tinged	Alcoholic	Alcoholic cirrhosis
5 F 33	0	800, clear yellow	2 wk.	3,000, clear yellow	Alcoholic	Cirrhosis; hydrothorax on the left; ascites
6 F 44	0	900, straw colored	2 wk.	3,000, clear yellow	Alcoholic	Cirrhosis; ascites; bilateral hydrothorax

The remaining 4 cases, as well as the preceding 2, are summarized in the accompanying table.

COMMENT

Analysis of these cases shows certain features worthy of comment. The ages of the patients ranged from 24 to 65 years. That one half of these patients were in the younger age group is explained by the fact that the criteria used for selection of cases tended to eliminate patients in the older age group. The cases were equally divided between men and women.

The pleural effusions frequently were impressive in amount, the total volumes ranging from 800 to 17,250 cc. The fluid was found in one instance in the right pleural cavity alone, in two instances only in the left and in three instances bilaterally. In terms of total volume

it was predominantly right sided in distribution. It had the characteristics of a transudate, with a specific gravity below 1.018 and a total protein content below 4 per cent. In the various protocols the fluids were described as clear yellow and straw colored, and once it was described as bile stained. As in Christian's case,[4] sanguineous fluid was found clinically only after repeated thoracenteses had been performed, the color having changed from a clear yellow to blood tinged. Fibrin strands were found occasionally. The known duration of the hydrothorax in all these cases was sufficiently long—from two weeks to months—to exclude the possibility of the fluid's having collected only during the agonal period.

Ascitic fluid was found at autopsy in all these cases, but in three instances it was much less in amount than the associated pleural collection. It is notable that the ascites usually elicited considerable clinical interest, whereas the larger pleural effusions frequently were ignored. As might be expected, moderate to excessive edema of the lower extremities occurred in the patients with massive acites. In none of the cases was there a significant degree of hydropericardium.

No conclusion can be drawn concerning the type of cirrhosis which is associated with hydrothorax. In 4 of our cases it was of the alcoholic type, in 1 it was acute yellow atrophy and in 1 it was of the unclassified type. No cases of biliary or pigmentary cirrhosis fulfilled the criteria for this series.

The explanation of the occurrence of the pleural fluid in cases of cirrhosis of the liver remains obscure. However, since all other causes for hydrothorax have been ruled out, we must attribute some causal relationship between the cirrhosis of the liver and the pleural fluid. In recent years Meigs[6] has called attention to the association of hydrothorax and ascites with certain large ovarian tumors. The theory has been advanced that fluid may pass from the abdominal cavity to the pleural cavity by way of the lymphatic vessels of the diaphragm. In substantiation of this hypothesis Meigs injected india ink into the peritoneal cavity and demonstrated its passage into the pleural cavity. India ink injected into the pleural cavity failed to appear in the peritoneal cavity. Additional support for this theory was found in the similarity of the fluid in the pleural and peritoneal cavities in certain cases, both fluids having similar protein content and electrophoretic distribution.

Benedetti,[3] while acknowledging the possibility of transdiaphragmatic passage of fluid, preferred in cases of cirrhosis to attribute the accumulation of pleural fluid to the increase in venous pressure in the azygos veins subsequent to the formation of collateral anastomoses between the portal and azygos systems.

One factor which has been difficult to evaluate is the relationship of hypoproteinemia and hypoalbuminemia to the production of massive

6. Meigs, J. V.; Armstrong, S. H., and Hamilton, H. H.: A Further Contribution to the Syndrome of Fibroma of the Ovary with Fluid in the Abdomen and Chest (Meigs' Syndrome), Am. J. Obst. & Gynec. 46:19, 1943.

hydrothorax.   While hypoproteinemia is frequently associated with cirrhosis of the liver, the relationship of hypoproteinemia to the production of hydrothorax is not so clearly defined.   Goffart[2] stated that in his experience hypoproteinemia exerts no constant or major influence on the production of hydrothorax.   In all our cases in which the determination was made, the level of the serum albumin was low.   However, similar cases of cirrhosis with low albumin and total protein levels are found frequently without a significant degree of hydrothorax.   Hence, hypoproteinemia and/or hypoalbuminemia may reasonably be excluded as the primary etiologic factor in the production of hydrothorax associated with cirrhosis.

Because the occurrence of hydrothorax during the course of cirrhosis is not common, a perplexing clinical problem may arise when these two conditions are associated.   The first case is typical of some of the problems.   Throughout the patient's stay in the hospital the presence of rapidly recurring massive hydrothorax dominated the clinical course of the disease, and the cirrhosis was regarded as an incidental finding. Cardiac failure, tuberculosis, intra-abdominal malignant tumor and tumor metastatic to bone were excluded by appropriate studies.   An intensive study, including repeated roentgenograms, bronchoscopy and numerous histologic sections of sediment of pleural fluid, was made in an attempt to detect a suspected bronchiogenic carcinoma.   In spite of the noncontributory results of the diagnostic procedures, the final clinical diagnosis was held to be bronchiogenic carcinoma with pleural metastases to account for the hydrothorax.

The second cited case presented an equally difficult diagnostic problem, since cirrhosis was not evident and the presenting signs and symptoms were those of a recurring hydrothorax.   Roentgenograms of the chest revealed no evidence of underlying pulmonary tuberculosis.   The diagnosis at this time was pleural effusion of tuberculous origin, and the patient was given rest in bed pending a report of inoculations of a guinea pig with sputum, gastric washings and pleural fluid.   Ten weeks later the clinical picture had become more complex, with the onset of the signs and symptoms of acute hepatic failure.   At this time less common diagnoses such as lupus erythematosus disseminatus, Hodgkin's disease, Pick's disease and hepatoma superimposed on cirrhosis of the liver were considered but not established.   The case came to autopsy with the diagnosis of pleural effusion and hepatic failure, both of undetermined origin.   The clinical confusion caused by this combination of symptoms is shown not only by the variety of diagnoses considered but also by the statement in the clinical record that "the appearance of .massive pleural effusion before the appearance of ascites is puzzling if the entire clinical course is to be explained on the basis of damage to the liver."   It is interesting also that the hydrothorax occurred ten weeks before the hepatic failure became evident.   Pathologically there was an old cirrhotic process present in the liver as well as a superimposed acute necrosis.

It is noteworthy that in Christian's case [4] diagnostic difficulties were encountered also. As he said,

- The diagnosis in this case, particularly after the development of the hemorrhagic fluid in the left pleural cavity with its rapid reaccumulation, was actively discussed by the staff. At first the diagnosis of cirrhosis of the liver was held. With pulmonary and pleural signs appearing, it was thought that these resulted from a complicating inflammation. When the pleural fluid was found bloody and reaccumulated so rapidly, diagnosis veered to neoplasm, presumably primary in liver, as none could be demonstrated elsewhere (negative roentgen-ray study of gastrointestinal tract; no evidence of prostatic tumor).

This discussion does not imply that an etiologic factor in hydrothorax other than cirrhosis of the liver should not be carefully searched for in these cases. Rather it is to be emphasized that when all other possible causes for the hydrothorax have been excluded the pleural fluid may reasonably be considered to be associated with the cirrhosis.

CONCLUSION

Massive hydrothorax with no etiologic basis other than cirrhosis of the liver is rare. Six cases are presented, 2 in detail. The precise mechanism of the accumulation of pleural fluid in cases of cirrhosis remains obscure. When these two conditions are associated, perplexing diagnostic problems arise. When the appropriate studies rule out other causes of massive hydrothorax, the pleural fluid may reasonably be considered to be associated with cirrhosis of the liver.

STEVENS-JOHNSON SYNDROME

Report of Nine Patients Treated with Sulfonamide Drugs or Penicillin

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STEVENS and Johnson [1] in 1922 described a "new" eruptive fever associated with stomatitis, ophthalmia, cutaneous eruption and constitutional symptoms. This syndrome is usually considered uncommon; we have seen but 15 patients with it out of 115,000 patients admitted to the hospital since September 1942, 6 of whom had only simple catarrhal conjunctivitis and are not included in this report. This syndrome deserves more emphasis because tragic complications of the eyes, consisting of corneal ulceration or panophthalmitis with partial or complete loss of vision, have been frequent in reported cases. Since these severe complications of the eyes did not occur in our 9 patients treated with sulfonamide drugs and/or penicillin, we feel that their cases should be reported.

Stevens-Johnson syndrome has been referred to as erythema multiforme bullosum with involvement of the mucous membranes of the eyes and mouth,[2] erythema exudativum multiforme with opthalmia and stomatitis [3] or severe erythema multiforme.[4]

1. Stevens, A. M., and Johnson, F. C.: New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child. 24:526 (Dec.) 1922.

2. Ageloff, H.: Erythema Multiforme Bullosum with Involvement of Mucous Membranes of Eyes and Mouth (Stevens-Johnson's Disease): Report of a Case, New England J. Med. 223:217 (Aug. 8) 1940.

3. Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis: Report on Two cases in Children with Certain Observations on Histopathology and Animal Inoculation, J. Pediat. 12:151 (Feb.) 1938.

4. Lever, W. F.: Severe Erythema Multiforme: Report of Two Cases of the Type Ectodermosis Erosiva Pluriorificialis, with Development of Cicatricial Conjunctivitis and Keratitis in One case, Arch. Dermat. & Syph. 49:47 (Jan.) 1944.

Bailey [5] expressed the belief that this syndrome was a form of erythema multiforme with severe lesions of the eyes. He reported 3 patients who had some loss of vision. Ginandes [6] in 1935 reviewed 9 cases. Seven of the patients became totally·blind, and the remaining 2 showed some impairment of vision. Lever [4] in 1944 gave an excellent bibliography and summary of the clinical manifestations of this syndrome and reported 2 cases. Conjunctivitis persisted in both cases, with development of conjunctival scarring and corneal opacities in 1.

The causation of this syndrome is unknown. Many factors have been suggested as playing a part; various micro-organisms and drugs having been blamed, including the sulfonamide drugs. Hemolytic Staphylococcus aureus and Vincent's organisms have been among the most commonly blamed bacteria. In our series, both organisms have been found, but it is our opinion that these are secondary invaders.

The syndrome consists in an acute illness accompanied with the appearance of vesicular, bullous and ulcerative lesions on the mucous membranes, most characteristically those of the eyes, nose, mouth, tracheobronchial tree, esophagus, anus and genitalia. Lesions of the skin may or may not be present, being either erythematopapular or vesiculobullous in nature, but when present are of the type seen in an ordinary case of erythema multiforme. The patients may be seriously ill, or they may have few systemic symptoms. Fever may or may not be present, and the degree of elevation of the temperature varies considerably. Recurrences have been frequent, and generally the later attacks are less severe than the initial one. Most of the patients are in the younger age group.

The symptomatology is protean. Almost all the mucous membranes have been reported to be ·the site of appearance of the lesions. Conjunctivitis, rhinitis, stomatitis, pharyngitis, tracheobronchitis, urethritis, balanitis, hematuria, generalized lymphadenopathy and splenomegaly and lesions of the anal mucosa have been reported.

With such a multiplicity of sites involved, the possibilities of complications are great. The most dramatic complications in the patients who survive are to be found in the eyes, where decided purulent conjunctivitis leads at times to the development of perforation of the cornea and the appearance of panophthalmitis, with total loss of vision, or to corneal scarring with diminution of the visual acuity or chronic conjunctivitis and the formation of symblepharon, with subsequent distor-

. 5. Bailey, J. H.: Lesions of Cornea and Conjunctiva in Erythema Exudativum Multiforme (Hebra): Report of Three Cases with Grave Ocular Sequelae, Arch. Ophth **6**:362 (Sept.) 1931.

6. Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia: Atypical Erythema Exudativum Multiforme (Stevens-Johnson Syndrome), Am. J. Dis. Child. **49**:1148 (May) 1935.

tion of the eyelids. Therefore, early diagnosis and institution of proper treatment to attempt to prevent permanent ocular involvement are imperative.

In consideration of the differential diagnosis, the most important conditions to be ruled out, as Lever indicated, are foot and mouth disease, Vincent's angina, drug eruptions, pemphigus, venereal penile lesions and urethritis.

Drug eruptions may be difficult to distinguish. The lesions may be identical in appearance, but the history, the notable systemic involvement and the course should aid in the clarification. In consideration of drug eruptions, it is of interest that the sulfonamide drugs have been implicated as precipitating factors or specific causes in some cases of erythema multiforme bullosum. The patient in case 7 had been given sulfadiazine several weeks prior to the onset of the Stevens-Johnson syndrome. He had experienced three previous attacks, prior to none of which had he received any sulfonamide drugs. The use of the sulfonamide compounds in our cases did not appear to aggravate the lesions but rather had the directly opposite effect.

The appearance of foot and mouth disease is clinically similar to that of the Stevens-Johnson syndrome. The differentiation depends on the inoculation of laboratory animals when foot and mouth disease is suspected, according to Klauder.[7]

Vincent's angina does not cause the large bullous lesions on the mucous membranes so characteristic of the Stevens-Johnson syndrome (fig. 3 *A*).

Pemphigus vulgaris has an entirely different onset and course than erythema multiforme bullosum.

Penile lesions require a dark field examination and serologic analysis of the blood, which revealed normality in our cases. The appearance of the rash on the skin, and the bullous involvement of other mucous membranes should establish the differential diagnosis.

Urethritis may be suspected in patients complaining of urinary symptoms but should offer no difficulty in the decision as to whether it is or is not a part of the general picture.

As a general rule, the prognosis in cases of Stevens-Johnson syndrome is favorable as regards life, only 4 fatal cases having been reported in the world's literature, according to Lever.

Until recently, treatment has consisted in supportive and symptomatic measures. Five cases have been reported in which either sulfonamide drugs or penicillin were employed in the treatment of the patients, 4 of

7. Klauder, J. V.: Ectodermosis Erosiva Pluriorificialis: Its Resemblance to the Human Form of Foot and Mouth Disease and Its Relation to Erythema Exudativum Multiforme, Arch. Dermat. & Syph. **36**:1067 (Nov.) 1937.

whom made complete recoveries. Givner[8] reported 2 cases of this syndrome, in both of which one of the sulfonamide drugs had been given therapeutically, and in both cases complete recovery ensued. He added a third case of a patient under treatment at the time his paper was being written. Erger[9] reported 1 case of a patient treated with sulfadiazine in whom corneal scarring developed, and Kove[10] reported the cases of 2 patients, both of whom made complete recovery, both of whom received sulfadiazine and 1 of whom had penicillin instilled in the eye in addition. To these we are adding reports of 9 cases of patients treated with either sulfonamide compounds or penicillin, 8 of whom made complete recovery. In the other patient chronic conjunctivitis and mild symblepharon developed but without evidence of corneal scarring.

REPORT OF CASES

CASE 1.—The patient was admitted to the hospital on Sept. 20, 1942, with a complaint of fever, headache, malaise and a nonproductive cough starting three days prior to admission and becoming progressively worse. He appeared moderately ill. There was a mucopurulent nasal discharge, slight scleral injection and mild cervical adenitis. The white blood cell count was 4,550, with 66 per cent polymorphonuclear cells. Urinalysis yielded normal results. A diagnosis of influenza was made. Five days later he was extremely ill, the temperature was 104 F., he was coughing considerably, the pharynx was inflamed and a single bulla was noted in the mouth and one on the skin. By the next morning there were present erosive stomatitis and pharyngitis, with some erythematous vesicles on the hands. He was given a blood transfusion and fluids intravenously. Bilateral severe purulent conjunctivitis rapidly developed, and his temperature remained near 104 F. Because of the seriousness of the illness, sulfadiazine therapy, consisting of administration of 4 Gm. initially and 1 Gm. every four hours, was started. Additional transfusions were given. Cultures of material taken from the mouth and eyes showed hemolytic Staph. aureus. Cultures of the blood were sterile. A roentgenogram of the chest showed increased pulmonary markings but no infiltration. Gradual improvement followed, with the eventual clearing of all the lesions except for mild persistent bilateral conjunctivitis, with no evidence of corneal opacities but with granulations of the lids and mild symblepharon. He was separated from the service eventually because of the chronic conjunctivitis and emotional instability.

CASE 2.—The patient, aged 25, was admitted to the hospital on Jan. 22, 1943, with a history of sore throat for one day. The tonsils presented a follicular exudate, and the temperature was 99.4 F. He was given sulfathiazole. Three days later large bullae developed in the mouth, and the following day there were conjunctivitis and papular and vesicular lesions on erythematous bases on the extremities. The

8. Givner, I., and Ageloff, H.: Stevens-Johnson Disease with Complete Visual Recovery, New York State J. Med. **41**:1762 (Sept. 1) 1941.

9. Erger, B. D.: Erythema Multiforme Pluriorificialis (Stevens-Johnson Disease), Mil. Surgeon **95**:308 (Oct.) 1944.

10. Kove, S.: Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis), Am. J. M. Sc. **210**:611 (Nov.) 1945.

white blood cell count was 11,600, with a polymorphonuclear content of 76 per cent. The urine was normal. A culture of material from the eyes showed Staphylococcus albus and Staph. aureus. On January 27, sulfadiazine was substituted for the sulfathiazole, and sulfathiazole ointment was ordered for the eyes. There was complete subsidence of all lesions except for the development of mild adhesions between the prepuce and glans penis.

CASE 3.—The patient, aged 18 years, was admitted to the hospital on Jan. 9, 1944, with the history of a sore throat for one week and a sore mouth and profuse discharge from the eyes for two days. He had had two previous similar attacks, in March and September 1943, the first being the worst. He appeared moderately ill. The temperature was 102.8 F. and the pulse rate 100. There were multiform erythematous lesions, chiefly papules and vesicles, on the palms, wrists and lower parts of both legs. There were a few vesicles on the lips, while the tongue, palate and buccal mucosa appeared gray and dull and displayed a few bullae. There was a profuse serofibrinous discharge bilaterally from the eyes, with definite chemosis and photophobia. The white blood cell count was 14,650, with a polymorphonuclear content of 83 per cent. The urine was normal, and smears were negative for Vincent's organisms but cultures of material from the throat were later reported to show beta hemolytic streptococcus and Streptococcus viridans. The sedimentation rate was 33 mm. in one hour. He was given sulfathiazole both orally and locally. After administration of a total of 12 Gm. of the drug his temperature was normal, and it remained so until he was discharged as cured on February 1.

CASE 4.—The patient, aged 22 years, was admitted to the hospital on Feb. 7, 1944, with a history of pain in the jaws, watering of the left eye and a penile sore for five days. He had experienced a similar attack the preceding year. The temperature was 99.6 F. and the pulse rate 100. There was an erosive stomatitis, conjunctivitis of the left eye and erosion of the glans penis. There were vesicles on erythematous bases on both hands. He was given sulfathiazole orally and sulfathiazole jelly for use in the eye. He was discharged as completely cured on Feb. 23, 1944.

CASE 5.—The patient, aged 28, was admitted to the hospital May 5, 1944 with a history of sore throat and mouth, with difficulty in swallowing, burning of the right eye and cough and fever for two days. He experienced a similar episode two years previously. The temperature was 99.6 F., there was mild bilateral conjunctivitis, the pharynx was inflamed and showed pronounced ulcerations and there was mild balanitis present. Cultures of material from the penis and eye showed a nonhemolytic Staph. aureus. The white blood cell count was 14,000, with a polymorphonuclear content of 76 per cent. The urine was normal. He was given sulfathiazole orally and sulfathiazole sesquihydrate drops in the eyes. There was a prompt subsidence of all lesions.

CASE 6.—The patient, aged 23, was admitted to the hospital on Jan. 29, 1945 with a history of difficulty in swallowing for three days. He was unable to eat solid food and could swallow liquids only with difficulty. He had noticed blisters on his arms and legs two days before his admission. Examination showed an acutely ill man, with a temperature of 102 F. and a pulse rate of 90. There were small bullae on erythematous bases scattered over the extremities, with a few on the neck, trunk, buttocks and penis and one at the anus. There were extensive ulcerations on the buccal mucosa, pharynx, tonsillar pillars, gums and lips, with fresh bullae on the pharynx. There was decided fetor oris. There was an erythematous area in the right eye at the outer canthus, but no ulcers were present.

A smear from the mouth showed Vincent's organisms, while culture of material from the penis showed Str. viridans. The zone of inhibition for the latter organism was only 24 mm. to 5.0 units of penicillin. Despite this, because of the severity of the clinical appearance, administration of penicillin by intramuscular injection was instituted. There was prompt response to therapy, and by February 6 the lesions were all healing. He was subsequently discharged as cured.

CASE 7.—The patient, aged 25, was admitted to the hospital on June 30, 1945. Two weeks previously he had received a course of sulfadiazine for four days. Three days before his present admission he noted a sore-mouth, pain on swallowing, a penile sore and pain on urination. These became worse, and vesicles developed on his arms and legs. He had had three previous attacks similar in nature. He was mildly ill, with a temperature of 100.6 F. The skin showed vesicular lesions of erythema multiforme on the extremities and on the penis. There was considerable ulceration on the gums, pharynx and nasal mucosa. The white blood cell count was 17,300, with a polymorphonuclear content of 78 per cent. The urine contained 3 to 4 pus cells per high power field. Culture of material from the mouth showed hemolytic Staph. aureus, with a 22 mm. zone of inhibition with 0.5 units and 38 mm. with 5.0 units of penicillin. Culture of material from the penis showed Str. viridans. The following day there was chemosis at the outer canthus of the right eye, and he was given penicillin jelly, 5,000 units per cubic centimeter, in a water-soluble base, to use in the eye. During the course of the next three weeks the lesions all healed.

CASE 8.—The patient, aged 27 years, was admitted to the hospital on March 30, 1945, with a history of having noticed several small ulcers in the mouth and on the lips four days before, followed by small blisters on the glans penis. He had had two attacks of similar nature in the past, in both of which the eyes were involved. Examination showed a moderately ill man, with a temperature of 102 F. and a pulse rate of 108. There were ulcerations of the lips and oral mucosa and several discrete lesions of the iris type on the glans penis. Culture of material from the mouth showed beta hemolytic streptococcus and Str. viridans. The penicillin cup test showed only a 16 mm. zone of inhibition with 0.5 units. The white blood cell count was 9,500, with a polymorphonuclear content of 77 per cent. The temperature promptly subsided to normal and remained so. Symptomatic therapy was given, but one month later there had been no particular improvement of the lesions. Starting on May 6, he was given penicillin intramuscularly to a total of 100,000 Oxford units. There was a notable almost immediate response, with complete healing.

He was readmitted on Aug. 24, 1945, with a sore mouth and penile blisters of four or five days' duration. At this time he was only mildly ill, with a temperature of 99.2 F., but there were extensive ulcerations of the buccal mucosa, with some membranous formation, and bullae were present on the penis and one on the skin of the chest. A smear from the mouth showed many fusiform bacilli and a few spirochetes. He was again given penicillin, and by September 6 all lesions had disappeared.

CASE 9.—An 18 year old youth was admitted to the hospital on May 6, 1945, with a history of having had a sore mouth for four days followed by the appearance of red spots and blisters on the chest, arms and penis and subsequently inflamed eyes. He appeared moderately ill and could hardly swallow. His temperature was 99.8 F. There were scattered erythematous lesions, with vesicles and crusting on the skin and penis. Pronounced ulcerations were present on the lips and in the mouth with membranous formation. There was also moderate bilateral conjunctivitis. The

white blood cell count was 10,800, with a polymorphonuclear content of 64 per cent. Culture of material from the throat showed Str. viridans and Staph. aureus, while culture of material from the eyes was sterile. He had had two previous similar episodes, at the ages of 14 and 16 years. He was given penicillin intramuscularly to a total of 460,000 units. His temperature rapidly returned to normal, and by May 23 all lesions had healed. On June 14, while still a patient, he had a recurrence of the lesions, which healed again only to have a fresh crop appear on June 30. On July 5 an ulcer was noted at the anus. When these lesions healed no further recurrences interrupted his convalescence, and he was discharged Aug. 20, 1945.

Fig. 1.—Type of ocular involvement.

Fig. 2.—Balanitis and ulceration.

COMMENT

The accompanying photographs (figs. 1, 2 and 3) illustrate typical lesions of this disease. Figure 1 shows the average type of ocular involvement in the 9 patients who received specific therapy. Note the tenacious membranous exudate in each canthus. Figure 3 *A* shows the bullae on the lips and mucous membrane, which occur early. Figure 3 *B* is of a later stage, when the bullae have ruptured. Figure 2 illustrates penile ulceration and balanitis.

Specifically, the treatment employed consisted in oral use of sulfonamide drugs in 5 patients, in 4 of whom sulfathiazole sesquihydrate drops

or sulfathiazole jelly were employed in the eyes. Three patients were given penicillin intramuscularly, usually with an initial dose of 30,000 Oxford units followed by 20,000 units every three hours to a total of 300,000 units. Penicillin jelly, with 5,000 units to 1 cc. of water-soluble base, was used in the eyes in 1 case. In addition to the use of sulfonamide drugs and penicillin, symptomatic measures were employed, consisting in gentle removal of the membranous conjunctival exudate with boric acid solution at frequent intervals. Hydrogen peroxide was used in a half-strength solution as a mouthwash, and the penile lesions were treated with compresses of sodium bicarbonate.
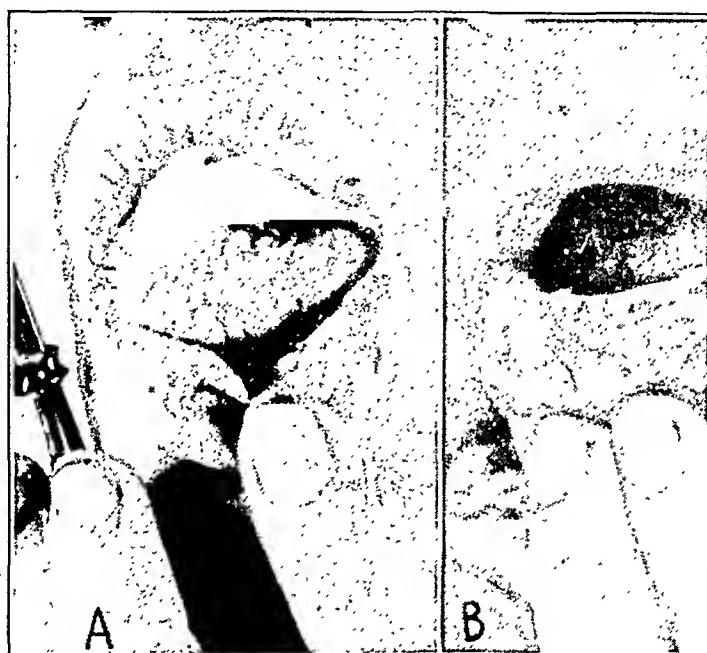
Fig. 3.—*A*, unruptured bullae; *B*, ulcerations from ruptured bullae.

CONCLUSIONS

Nine cases of Stevens-Johnson syndrome have been presented. Five patients were treated with sulfonamide drugs, and 4 patients were treated with penicillin, either systemically or topically or both. Complete recovery without sequelae occurred in all but 1 case. In this case a mild conjunctivitis developed with slight symblepharon but no corneal involvement. Enthusiasm for any type of therapy in this syndrome must be tempered by the fact that the severity of the clinical course varies greatly and that recovery without complications of the eyes is not uncommon. Six of our 9 patients experienced at least one previous attack without permanent ocular damage.

The results of this small series suggest but do not prove that a method of treatment including the use of sulfonamide compounds and/or penicillin might be beneficial in prevention of the tragic complications which so often accompany or follow this disease.

PNEUMONIA IN OLD AGE

Active Immunization Against Pneumonia with Pneumococcus Polysaccharide; Results of a Six Year Study

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EVER since the discovery of the causative agent of pneumonia, its high toll of death has stimulated studies on active immunization against this disease. The experiments, however, when done on human beings were always of short terms. It seemed, therefore, that there was a need for a long term experiment on active immunization against pneumonia. The year by year fluctuations in the incidence and mortality rates might have distorted the results of even the most carefully controlled immunization studies if carried on only for a short period. The perusal of the literature proves that this is exactly what happened; all these experiments, whether done on a large or small scale with vaccines or pneumococcus polysaccharides, were conducted only for one or two years. This is one of the reasons why they contain such contradictory results, contradictory sometimes even within the scope of the same experiment.

Furthermore, it seemed· evident from the beginning that if a group was chosen with the highest incidence and mortality rates and with the possibility of continuous observation, hospitalization and reexamination much more conclusive data could be obtained. That was the reason the present study was undertaken in 1937 at the Medical Division of the former Central and Neurological Hospital and the New York City Home and continued at the Goldwater Memorial Hospital, where higher age groups are treated. Within the period of six years it involved about 10,000 persons, immunized and controlled combined, and its purpose, besides immunization of human subjects, was to observe the comparative clinical and pathologic features of pneumonia in the immunized patients

as compared with those of the disease in the control group, to examine the antigenic effect of the polysaccharides used in this study against experimental pneumococcic infection in mice and to determine the presence of circulating antibodies in those who were immunized.

HISTORY AND LITERATURE OF ACTIVE IMMUNIZATION

Vaccines.—Wright (1913) and others [1] used a nontyped vaccine for immunization against pneumonia in the South African coal mines. The incidence of the disease, as compared with that of the previous year, dropped from 4 to 0.28 per cent and the mortality rate from 0.31 to 0.14 per cent. Maynard [2] (1913) and, later, Lister [3] (1916) used types I, II and III vaccines in the same mines. Both reported a substantial decrease in the incidence and mortality rates. Cecil and his associates [4] (1918, 1920 and 1921) used in three different military camps Whitmore's lipovaccine, an emulsion of types I, II and III pneumococci in oil. The incidence of pneumonia among the inoculated patients was almost one fourth of that among the noninoculated ones.

Further experiments with vaccines on animals have been reported by Barach [5] and Barach and Soroka.[6] Recently, Smillie [7] used types I and II vaccines for the immunization of 590 patients and 40 attendants in an epidemic of pneumonia in the Veterans Administration Hospital at Bedford, Mass. He paid more attention to the epidemiologic and pneumococcus-carrier aspect of the problem. Nevertheless, he felt that the immunization prevented the spread of the epidemic. The vaccine he used was prepared from pneumococci killed by solution of formaldehyde instead of heat, and he used young smooth cultures made with a large amount of inoculum for rapid growth and interrupted before the peak of growth. He gave three injections (0.5, 1.0 and 1.0 cc.) in weekly intervals subcutaneously. No local reaction was noted. Results were encouraging.

1. Wright, A. E.; Morgan, W. P.; Colebrook, E., and Dodgson, R. W.: Observation on Prophylactic Inoculations Against Pneumococcic Infection, London, 1913; Lancet **1**:87, 1914.

2. Maynard, G. D.: An Enquiry into the Etiology, Manifestations, and Prevention of Pneumonia Amongst Natives on the Rand, Recruited from Tropical Areas, Publication 1, South African Institute for Medical Research, Johannesburg, 1913.

3. Lister, F. S.: Experimental Study of Prophylactic Inoculation Against Pneumococcal Infection in the Rabbit and Man, Publication 8, South African Institute for Medical Research, Johannesburg, 1916.

4. Cecil, R. L., and Austin, J. H.: J. Exper. Med. **28**:19, 1918.

5. Barach, A. L.: J. Exper. Med. **53**:567, 1931; Proc. Soc. Exper. Biol. & Med. **25**:558, 1928.

6. Barach, A. L., and Soroka, M. J.: J. Exper. Med. **48**:83, 1928.

7. Smillie, W. G.: Am. J. Hyg. **24**:532, 1936.

Summarizing the experience of the different authors who used living or killed pneumococci in immunizing human beings and animals, we might say that the results are contradictory. Some authors claimed that the smallest doses usually are sufficient to produce high immunity while high doses stimulate less antibody production, besides causing toxic effects. They reported that in rabbits, after five hours, immune bodies were present in a small degree and that their titer increased after three days, stayed at a peak for one month and was demonstrable for ten months. In mice the immunization succeeded only after large doses had been given subcutaneously or intravenously. In human beings three subcutaneous injections were given in four to eight day intervals, with occasional bad reactions. Most authors noted, besides the specific immunity against types used, protection against other pneumococcic infections. In the experiments on human beings some recorded an apparent decrease in the number of infections of the upper respiratory tract.

Polysaccharides.—Auld [8] and Kraus [9] discovered in the same year (1897), independently, that the germ-free filtrates of certain bacterial cultures contain a substance with antigenic properties—Auld in the cultures of pneumococci and Kraus in cultures of organisms causing typhoid, cholera and bubonic plague. Dochez and Avery [10] (1917) called this substance the "specific soluble substance" and have shown that its presence is due not to bacterial disintegration but to extrusion into the medium of bacterial substances during the life process of the organism. They also demonstrated the presence of this substance in the serum and urine of patients with pneumonia and showed that its presence in abundance indicates a grave prognosis.

Heidelberger and Avery [11] (1923) gave evidence that these nonprotein precipitable substances were polysaccharides and that the combination of the carbon, hydrogen and oxygen to form various percentages of carboxyl, acetyl and other radicals and the combination of these groups with different sugars determine the specificity of the types of pneumococci. They found that the polysaccharide of the type I pneumococci had no antigenic effect, while other authors, with different methods of isolation, demonstrated the antigenic effect of this as well as of the other capsular pneumococcus polysaccharides.[12]

8. Auld, A. G.: Brit. M. J. **1**:775, 1897.

9. Kraus, R.: Wien. klin. Wchnschr. **10**:736, 1897.

10. Dochez, A. R., and Avery, O. T.: J. Exper. Med. **26**:477, 1917.

11. Heidelberger, M., and Avery, O. T.: J. Exper. Med. **38**:73, 1923.

12. Chemically similar substances, i. e., polysaccharides, were isolated by several authors in all sorts of bacteria and found to be serologically active. A partial list follows: Meningococcus; Streptococcus; Gonococcus; Hemophilus influenzae; Pasteurella group; Brucella group; Aerobacter aerogenes; Proteus vulgaris; Bacillus anthracis; spirochetes; Rickettsia, Monilia, Salmonella and Shigella groups; yeasts, and fungi.

Felton in 1932 [13] isolated from pneumococci a water-soluble substance which he found antigenic for mice. He and his collaborators [14] reported later (1938) experiments in immunization on a large number of persons in the Civilian Conservation Camps. The first three experiments were not considered sufficiently controlled to warrant any definite conclusions. In the fourth experiment, inoculations were done on 10,740 men in New England and on 18,494 men in camps on the West Coast. The duration of their observation was short, in some cases 68.3 days and in others 117.4 days.

The incidence rate in the camps on the West Coast was 1.73 in the inoculated persons against 15.96 in the noninoculated group per thousand years of life. The camps in New England showed an incidence of 4.32 per thousand in the inoculated group against 7.28 in the control group. In other words, the incidence in the camps on the West Coast was about nine times higher in the control group than that in the inoculated group, while in the camps in New England it was only about twice as high. According to Felton and his co-workers, "the difference in case ratio between inoculated enrollees in the New England camps and those in the West Coast camps cannot be definitely accounted for." Owing to the circumstances inherent in their experiments, the number of deaths was considered too low to justify any conclusions with regard to the effect of the antigen on the mortality or case fatality rates.

In previous papers,[15] we reported on the results of two years' immunization of 1,750 persons (with 1,870 controls) with types I and II polysaccharides. Among the immunized persons there were 23 patients with pneumonia, making the incidence rate 13.13 per thousand, while among the controls there were 104 patients with pneumonia, with a rate of 55.66 per thousand. The mortality rate in the immunized group was 7.4 per thousand against 35.8 per thousand among the controls.

EXPERIMENTS ON ANIMALS

Methods and Materials.—In the beginning of this study the polysaccharide was prepared by the following method: Broth cultures of type I and type II pneumococci were centrifuged for forty-eight hours. The supernatant fluid was submitted to ultrafiltration. The presence of the soluble specific substance was precipitated by the repeated use of large volumes of alcohol in a reaction which was neutral to slightly acid. The soluble carbohydrates were then tested for their purity and

13. Felton, L. D.: J. Immunol. **23**:405, 1932.

14. Felton, L. D.; Ekwurtzel, G. M.; Simmons, J. S., and Dublin, L. I.: Pub. Health Rep. **53**:1855, 1938.

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antigenic properties. The material employed was a combination of types I and II polysaccharides. Chemically, the dextrose and nitrogen content was approximately that of the specific soluble substance of Heidelberger and Avery.

Later a pooled polysaccharide of types I, II and III pneumococci, prepared in the laboratory of the National Institute of Health by Felton, according to his calcium phosphate methods, was used.

To test the antigenic property of this antigen, mice in groups of 20 were given injections of 0.5 cc. of 1:1,000,000 dilution containing 0.0005 mg. of active substance, and eight days later dilution of 1:100; 1:500; 1:1,000; 1:10,000, and 1:100,000 of pneumococcus cultures, representing five million, one million, five hundred thousand, fifty thousand and five thousand lethal doses respectively, were injected intraperitoneally. Protection against type I, type II and type III cultures was tested separately. Results of the titrations can be seen in table 1.

Against type I in dilutions of 1:100 (five million lethal doses) 8 mice out of 20 were protected, while more than 50 per cent of the mice

TABLE 1.—*Antigenic Effect of Types I, II and III Pneumococcus Polysaccharide in Mice*

Titration against 0.5 cc. of dilutions of cultures, specified below, eight days after intraperitoneal injection of 0.5 cc. of 1:1,000,000 dilution of polysaccharide.

Immunized Animals—Rate of Survival Among 20 Inoculated Mice														
Type I Culture Dilutions					Type II Culture Dilutions					Type III Culture Dilutions				
1:100	1:500	1:1,000	1:10,000	1:100,000	1:100	1:500	1:1,000	1:10,000	1:100,000	1:100	1:500	1:1,000	1:10,000	1:100,000
8	10	11	13	20	6	8	10	20	20	7	9	11	12	20

Control Animals—Hours of Survival Among Controls														
10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}
16	24	22	24	24	18	18	15	20	22	20	24	22	18	20
18	22	24	24	24	20	18	20	22	24	22	24	22	20	22
16	24	24	22	S*	16	18	18	20	S*	22	24	22	18	S*

* S indicates survival of animal.

survived injections of five hundred thousand lethal doses. Protection against cultures of types II and III was somewhat lower, but, generally speaking, protection against all three types was found in 50 per cent of the mice against five hundred thousand lethal doses. The survival time of the nonimmunized animals is given in the lower part of the same table in which the first line represents the culture dilutions (in logarithmic series), the number below them represents the survival time in hours and "survival" indicates survival of the control animals. The figures show that 1 animal survived in the 10^{-9} dilution in all three titrations. The survival time of all other animals varied between sixteen and twenty-two hours.

EXPERIMENTS ON HUMAN BEINGS

Materials.—For human beings the same antigens were used, in the first two years a pooled polysaccharide of types I and II pneumococci and in the following

years a polysaccharide of types I, II and III pneumococci. (For methods of preparation see previous parts of this study and Felton's several publications.[16]).

Each year in the pneumonia season a number of persons, selected at random, have been given injections of 0.5 cc. of this substance subcutaneously in the deltoid region. A total of 5,750 were immunized, and 5,153 were kept as controls. The previous history of each person was taken, with special reference to antecedent pneumonia or infection of the upper respiratory tract. On 400 persons taken at random the mouse-protective value of 0.10 cc. of blood serums, withdrawn before and fourteen days after immunization, was tested (for results see following paragraphs). The preliminary work included quantitative and qualitative blood cell counts. We kept records of previous physical examinations, temperature, pulse rate and blood pressure of the immunized persons. Eventual local or general reactions were noted in the protocols, in which the aforementioned data and further information as to the contraction of pneumonia or colds or other diseases were recorded. The records of the controls were handled in the same way. Every person who contracted pneumonia was transferred from the New York City Home

TABLE 2.—*Age Distribution Among the Immunized and Control Group*

Age, Yr.	Immunized Patients (Basis of 5,750), %	Controls (Basis of 5,153), %
Under 40 to 49	1.5	3.9
50 to 59	18.0	19.0
60 to 69	36.5	37.0
70 to 79	30.5	31.6
80 and over	13.5	8.5
Total	100.0	100.0

to Goldwater Memorial Hospital, where it was noted whether he belonged to the immunized or to the control group. Thus the features of the disease and its course, length and outcome in the two groups were observed.

The age distribution in the two groups was about the same, except that there were somewhat more persons in the oldest and somewhat less in the youngest group among the controls. Thirteen per cent were over 80 years, 30 per cent between 70 and 79, 37 per cent between 60 and 69, 18 per cent between 50 and 59 and 2 per cent between 40 and 49 in both groups (table 2). For equalizing purposes, we checked the general mortality rates from all causes except pneumonia in both groups and found that in the immunized group it was 91 and in the control group 89 per thousand.

Results of the Titration of the Blood Serums Before and After Immunizations.—Four hundred persons were selected at random; the only basis of selection was that in age they should be representative of the whole group. About 10 cc. of blood was withdrawn before and fourteen days after immunization and the antibody content tested separately against logarithmic series of dilutions of fresh type I and type II pneumococcus cultures in mice, in the usual manner. As the titrations show in tables 3 and 4, before immunization, protection was

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16. Felton, L. D.; Kauffmann, G., and Stahl, H.: J. Bact. **29**:149, 1935. Felton, L. D.; Sutliff, W. D., and Steele, B. F.: J. Infect. Dis. **56**:101, 1935.

afforded against lethal doses with a weighted mean of one hundred and six and after immunization, against one hundred and two thousand, one hundred and seventy lethal doses of type I pneumococci, which means roughly a thousandfold (nine hundred and sixty-four) increase in protection. As regards type II pneumococci, before immunization there

TABLE 3.—*Protective Titer of 0.1 cc. of Human Blood Serums of 400 Persons Before and After Immunization to Type I Pneumococci*

				Before Immunization				Weighted Mean Lethal Dose,* 106
Lethal doses	0	1	10	100	1,000 10,000 100,000 1,000,000			
Persons in each group	265	4	6	5	112	7	1	0	Total 400	Positive reactors, 135 (34%) Negative reactors, 265 (66%)

				After Immunization				Weighted Mean Lethal Dose,* 102,170
Lethal doses	0	1	10	100	1,000 10,000 100,000 1,000,000			
Persons in each group	121	0	5	3	18	15	217	21	Total 400	Positive reactors, 278 (69%) Negative reactors, 122 (31%)

* Key: Weighted mean lethal dose $= \dfrac{\Sigma XY}{n}$. Σ indicates the sum total; X, the number of persons in each group; Y, the number of lethal doses, and n, the total number of persons.

was protection against lethal doses with a weighted mean of two hundred and thirty-three; after immunization this showed an increase to seventy-seven thousand, eight hundred and twelve lethal doses (a three hundred and forty-four fold increase).

TABLE 4.—*Protective Titer of 0.1 cc. of Human Blood Serums of 400 Persons Before and After Immunization to Type II Pneumococci*

				Before Immunization				Weighted Mean Lethal Rose,* 233
Lethal doses	0	1	10	100	1,000 10,000 100,000 1,000,000			
Persons in each group	280	3	23	31	60	3	0	0	Total 400	Negative reactors, 280 (70%) Positive reactors, 120 (30%)

				After Immunization				Weighted Mean Lethal Dose,* 77,812
Lethal doses	0	1	10	100	1,000 10,000 100,000 1,000,000			
Persons in each group	90	3	0	8	14	21	259	5	Total 400	Negative reactors, 90 (23%) Positive reactors, 310 (77%)

* For key, see footnote at bottom of table 3.

Effect of Immunization on the Incidence and Mortality Rates (table 5).—During the period of six years 5,750 persons were immunized and 5,153 observed as controls. There were 99 cases of pneumonia in the first group, meaning an incidence rate of 12.2 per thousand for a six year period. In the control group the number of cases of pneumonia was 227, making an incidence rate of 44 per thousand for a six year period. The mortality rate among the immunized patients was 6.2 per thousand against 19.0 per thousand in the control group, also for a

period of six years. The examination of the figures indicates that there is a great year by year fluctuation in the incidence as well as in the mortality rates of both groups. The significance of this was touched on in the introductory part of this paper and will be elaborated on in the discussion.

TABLE 5.—*Incidence of Pneumonia and Mortality Rates Among Immunized Persons and Controls at Goldwater Memorial Hospital*

	Immunized					Controls				
Year	No. of Immu- nized Persons	No. of Cases of Pneu- monia	Inci- dence per 1,000	Rates No. of Deaths	Mor- tality Rates per 1,000	No. of Con- trols	No. of Cases of Pneu- monia	Inci- dence per 1,000	No. of Deaths	Mor- tality Rates per 1,000
1st (1937-1938)	1,000	14	14	8	8	1,120	63	56	47	42
2d (1938-1939)	750	9	12	5	6.6	750	41	55	20	26.6
3d (1939-1940)	900	18	20	7	7.7	850	25	29.4	9	10.6
4th (1940-1941)	950	19	20	6	6.3	850	23	27	8	9.4
5th (1941-1942)	1,100	18	16.3	5	4.5	800	38	47.5	8	11.2
6th (1942-1943)	1,050	21	20	9	4.3	783	37	47.2	6	7.6
Totals of 6 yr.	5,750	99	17.2	40	6.2	5,153	227	44	98	19

Local and General Reactions.—In 5 per cent of the immunized persons we noted reactions at the site of the injection, evidenced by redness and warmth of the skin. Two in 1,000 (altogether 12) had general reactions in the form of malaise and temperatures between 100 and 101 F. None of these reactions lasted longer than forty-eight hours. Reactions were equal in frequency in the group in which Felton's polysaccharide was injected and in the one in which ours was used.

TABLE 6.—*Length of Protection*

		Number of Cases	
Days from Inoculation to Onset of Pneumonia		Immunized	Controls
November to December.................	1 to 60	4	19
January to February.................	61 to 120	3	28
March to April.................	121 to 180	5	43
May to June.................	181 to 240	6	25
July to August.................	241 to 300	4	12
September to October.................	301 to 360	9	13
November to December.................	361 to 420	17	17
January to February.................	421 to 480	26	25
March to April.................	481 to 540	25	45

The Length of Protection.—In table 6 and in the chart the number of days which elapsed between immunization and the onset of pneumonia is plotted against the number of cases of pneumonia in every sixty day period, the basis being the means of six years' figures starting with the months of November to December. Similarly, the mean numbers of cases of pneumonia in the same sixty day periods in the control group are charted. In the immunized group 4 cases of pneumonia occurred

during the first sixty day period and 3 in the next sixty days, and gradually the figures increased in each following period, as can be seen from the almost straight ascending line of the chart. The interrupted line of the chart, representing the control group, shows a different trend, indicating the customary fluctuations in the incidence rate of pneumonia in the different seasons of the year. This confirms the
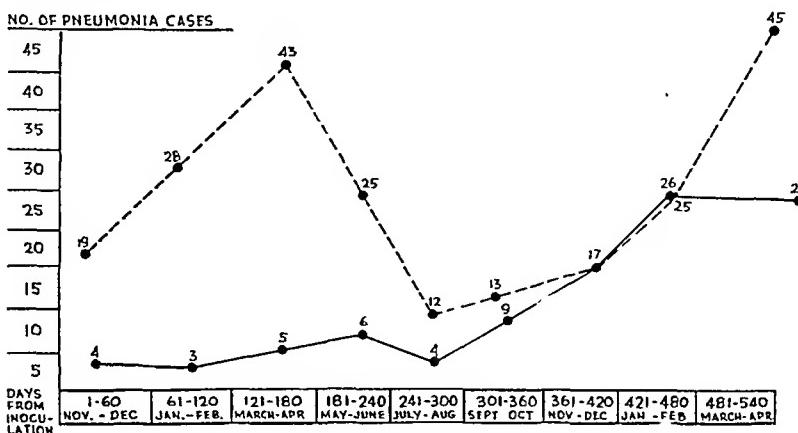
Interval between immunization and onset of pneumonia. The unbroken line indicates the number of cases of pneumonia as a mean of the six year period in every sixty days after immunization. The broken line indicates the same in the corresponding sixty day periods of the year among the controls.

impression gained from the month by month figures obtained in the first two years of this study, when also comparatively less cases of pneumonia occurred in the first three quarters of the year, after immunizations, than in the later periods.

COMPARISON OF CLINICAL AND PATHOLOGIC FEATURES OF PNEUMONIA IN THE TWO GROUPS

Lobar and Lobular Pneumonias.—There were 27 cases of lobar (8 deaths) and 72 of lobular (23 deaths) pneumonia found in the immunized group. Among the 227 cases of pneumonia among the controls, 67 were cases of lobar pneumonia, with 32 deaths, and 160 were of lobular pneumonia, with 66 deaths.

The Severity of the Disease in the Two Groups.—The following criteria were used to gage the severity of the disease (table 7):

A. Fatality Rates in Cases: The mortality rate in the immunized group was 40 per cent and in the controls 47 per cent, a difference which is statistically without significance.

B. The Extent of the Disease: In the immunized group only one lobe was involved in 23 out of 27 cases of lobar pneumonia (85 per cent) and in 4 cases two or more lobes were consolidated, while among the 67 with lobar pneumonia among the controls in 45 cases (67 per cent) only one lobe and in 22 cases two or more lobes showed roentgenographic signs of consolidation.

C. Bacteremia: Bacteremia was found in 8 cases among the immunized (8 per cent) and in 34 cases among the controls (14.9 per cent; table 9).

D. Duration of the Disease: The average duration of fever in the immunized group was two days in 28 per cent, four days in 32 per cent, eight days in 25 per cent, fourteen days in 10 per cent and more than fourteen days in 5 per cent of the patients who recovered. In the control group the duration of fever was two days in 20 per cent, four days in 27 per cent, eight days in 19 per cent, fourteen days in 23 per cent and more than fourteen days in 16 per cent. The length of time until roentgenologic resolution was completed in the immunized group was one week in 21 per cent, two weeks in 29 per cent, three weeks in 35 per cent, four

TABLE 7—*Comparative Analysis of Clinical Features in 326 Cases of Pneumonia Among the Immunized Patients and Controls*

	Average Duration of Fever in Patients Who Recovered, Days	Average Time Until Resolution by Roentgen Rays, Wk.	White Blood Cell Count, Average	Average Time for White Blood Cell Count to Come Down Below 8,000, Days	Extent of Process; Lobar or Lobular	Number of Lobes Involved Among Patients with Lobar Pneumonia
Immunized patients (fatality rate 40%)	2 (28%) 4 (32%) 8 (25%) 14 (10%) 14+ (5%)	1 (21%) 2 (29%) 3 (35%) 4 (13%) Unresolved (2%)	15,200	2 (27%) 4 (33%) 8 (21%) 8+ (19%)	27 lobar 72 lobular	1 (23 cases) 1+ (4 cases)
Controls (fatality rate 47%)	2 (20%) 4 (22%) 8 (19%) 14 (23%) 14+ (16%)	1 (15%) 2 (27%) 3 (38%) 4 (15%) Unresolved (5%)	14,800	2 (15%) 4 (29%) 8 (23%) 8+ (33%)	67 lobar 160 lobular	1 (45 cases) 1+ (22 cases)

weeks in 13 per cent; 2 per cent were unresolved. In the control group roentgenologic resolution required one week in 15 per cent, two weeks in 27 per cent, three weeks in 38 per cent and four weeks in 15 per cent; in 5 per cent of the cases the pneumonia was unresolved. In the immunized group the time required for the blood cell count to come down from an average of 15,200 to normal (below 8,000) was two days in 27 per cent, four days in 33 per cent, eight days in 21 per cent and more than eight days in 19 per cent. In the control group it came down from an average of 14,800 to less than 8,000 in two days in 15 per cent, in four days in 29 per cent, in eight days in 23 per cent and in more than eight days in 33 per cent of the cases.

E. Toxemia: Toxemia was found to be strikingly more frequent among the controls than in the immunized group. Abdominal distention was present in 8 per cent of the nonimmunized and in 2 per cent of the immunized group. Circulatory collapse, evidenced by an imperceptible uncountable pulse rate, low blood pressure and clamminess and ashen

color of the skin, was seen in 4 per cent of the controls and in 2 per cent of the immunized group.

COMPARATIVE FREQUENCY OF COMPLICATIONS

No substantial difference was found in the frequency of pleural effusions, empyemas, spontaneous pneumothoraxes and a number of

TABLE 8—*Comparative Frequency of Complications in Immunized and Control Groups (in Per Cent of Cases of Pneumonia)*

Complications	Immunized Persons, %	Controls, %
Pleural effusions	8	7
Empyema	4	7
Spontaneous pneumothorax	2	3
Atelectasis	3	2
Secondary purulent infection of air passage	5	7
Bronchiectasis	1	1
Unresolved pneumonia	2	5
Formation of pulmonary abscess	1	2
Uremia	3	5
Toxemia	2	6
Relapses	1	4

other complications as listed in table 8. It should be noted, however, that 2 cases of unresolved pneumonia, 2 cases of toxemia and 1 relapse occurred in the immunized group as compared with 5 cases of unresolved pneumonia, 6 cases of toxemia and 4 relapses in the control group.

TABLE 9.—*Distribution of Types Among the Cases of Pneumonia*

Type	99 Immunized		227 Controls	
	Number of Cases	Number of Bacteremias	Number of Cases	Number of Bacteremias
I	1	..	11	4
II	..	..	9	3
III	2	1	13	5
IV	3	1	9	1
V	2	1	7	3
VI	1	..	2	..
VII	2	1	6	2
VIII	3	..	4	2
IX	1	..	2	1
X	..	..	..	..
XI	..	..	..	..
XII	..	..	1	..
XIII	..	..	2	1
XIV	2	1	3	2
XV	..	..	..	..
XVI	1	..	..	..
XVII	..	..	..	..
XVIII	2	..	2	..
XIX	2	1	2	1
All other types	12	2	23	9
Total	34	8	96	34

Types of Pneumococci.—As can be seen from table 9, there were 3 cases of pneumonia caused by types I, II and III pneumococci among the 99 patients with pneumonia in the immunized group, making a rate

of 30.3 per thousand persons. Among the 227 patients with pneumonia in the control group, in 33 cases types I, II and III pneumococci were found, making a rate of 145.3 per thousand persons. Higher types were found in 31 cases in the immunized group (99 cases of pneumonia), making a rate of 313 per thousand persons. In the control group the higher types were found in 63 cases, making a rate of 277 per thousand. In other words, there were considerably more cases of pneumonia caused by types I, II and III pneumococci in the control than in the immunized group, while the percentage of the higher types was somewhat elevated in the immunized as compared with that in the control group.

OBSERVATIONS AT AUTOPSY AMONG THE IMMUNIZED AS COMPARED
WITH THE CONTROL GROUP

Twenty-six autopsies were performed on patients who died of pneumonia among the immunized group. The data obtained from 7 of these were published in detail in a preliminary report of this study.[14] From the observations made at these autopsies and at autopsies performed since then, it is evident that there is no appreciable difference between these results and those of 59 autopsies performed among the controls except in two points: in the extent of the process of pneumonia and in the frequency of some of the complications. More than one lobe was involved in 18 per cent of the immunized and in 34 per cent of the control group. Pericarditis was found in 7.2 per cent of the immunized patients and in 16.2 per cent of the controls. No difference was found between the two groups in the percentage of pleural effusions, empyemas, spontaneous pneumothoraxes and atelectasiae. Instances of unresolved pneumonia were found in 2 per cent of the cases in the immunized group at autopsy and in 5 per cent of the cases in the control group.

COMMENTS

This work of six years' immunization against pneumococcic infection submits additional evidence on the antigenic property of the capsular polysaccharide. That property was demonstrated previously by several authors but questioned by others. An effort was made here to eliminate one source of error—the year to year fluctuations of incidence and mortality rates—by continuing the experiments for a longer period. The results seem to corroborate the positive results of previous short term experiments. It is indicated that types I, II and III capsular polysaccharide, used here, gave protection in mice against an average of five hundred thousand lethal doses of homologous cultures, and it lowered the incidence rate of pneumonia in 5,750 immunized persons to 17.2 per thousand as compared with 44 per thousand among approximately the same number of controls. Similarly, it decreased the mortality

rate among the immunized persons to 6.2 per thousand as compared with 19 per thousand among the controls. The incidence of types I, II and III pneumococcic infections was considerably less in the immunized patients than in the control group: 30.3 per thousand against 145.3 per thousand. On the other hand, the percentage of instances of pneumonia caused by pneumococci higher than type III was somewhat elevated in the immunized persons as compared with that in the control group. These data are of significance since the antigen used in this study was in the first two years a type I and II and the following four years a type I, II and III polysaccharide.

In the blood of 400 of the immunized persons an average of a thousandfold increase of the mouse protective titer against type I and a three hundred and forty-four fold increase against type II pneumococci was demonstrated, as compared with the titer before immunization. It should also be noted that a certain percentage of the immunized patients failed to show the presence of antibodies either before or after immunization, an observation first pointed out by Felton, who also indicated that this inability to produce antibodies might have a bearing on the failure of resistance of certain persons to pneumococcic infection.

Attention was focused in this study on the comparative clinical and postmortem features of pneumonia among the immunized patients and the controls.

The question at this phase of the study was this: Did the antigen modify the picture of pneumonia in the group under investigation? The data presented here indicate that in both groups the usual features of pneumonia in old age were found at the bedside as well as on the table at autopsy. There was a difference, however, in certain points; the percentage of bacteremia, toxemia and metastatic invasion of other lobes or organs and the percentage of certain complications were higher among the controls than among the immunized persons. Since the number of cases of pneumonia was not large enough to draw final conclusions, further observations are necessary to answer the aforementioned question.

What is then the practical significance of immunization against pneumonia? Who should be immunized? It is clear that immunization of the general population in the present circumstances would not be practical. There is, however, justification and moreover a necessity for the use of polysaccharides where high incidence rates of pneumonia prevail, as in epidemics, in institutions, especially in homes for the aged, and generally in persons of old age or in those with a tendency to have annually or biannually recurring pneumonia. Even if, as the data presented here indicate, the protection afforded lasts only for ten to twelve months, its application seems to be justified in these cases.

SUMMARY AND CONCLUSIONS

1. The results of immunizations against pneumonia for a period of six years with a polyvalent type I and II and, later, type I, II and III pneumococcus polysaccharide are reported; 5,750 persons were immunized and 5,153 kept as controls.

2. During the total period of observation, the number of cases of pneumonia among the immunized persons was 99, making the incidence rate 17.2 per thousand. Two hundred and twenty-seven cases of pneumonia occurred within the same period in the control group, which equals an incidence rate of 44 per thousand. The number of deaths due to pneumonia in the immunized group was 40, with a mortality rate of 6.2 per thousand as compared with 98 deaths due to pneumonia (making a death rate of 19.0 per thousand) among the controls.

3. The antigenicity of polysaccharides was tested in mice separately against dilutions of types I, II and III pneumococcus cultures. Protection was found against an average of five hundred thousand lethal doses in 50 per cent of the animals.

4. The blood serums of 400 persons of the immunized group showed an average of a thousandfold increase in their protective body titer against type I and a three hundred and forty-four fold increase against type II pneumococcus cultures.

5. The clinical and pathologic picture of pneumonia in the two groups (immunized and controls) was generally the same. There were, however, relatively more bacteremias, toxemias, effusions, empyemas and cases of unresolved and relapsing pneumonia in the controls than in the immunized group. Similarly, there was a difference in the distribution of types in the two groups: more cases of types I, II and III occurred among the controls than among the immunized persons, while the incidence of the higher types was increased in the immunized group as compared with that in the controls.

6. Active immunization in epidemics of pneumonia, in persons in institutions, in elderly persons and in those who have a tendency to recurring pneumonia is suggested.

PRIMARY CARCINOMA OF THE LIVER

A Study of Thirty-One Cases

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PRIMARY carcinoma of the liver is a rare disease. In 1926 Counseller and McIndoe [1] reported 5 instances of this condition in 5,976 necropsies at the Mayo Clinic, and shortly thereafter they reported another.[2] Since that time, 25 additional cases of primary malignant growth of the liver have been discovered at necropsy at the Mayo Clinic. The present study is concerned with these 31 cases.

HISTORIC SURVEY

Rokitansky [3] is credited with being one of the earliest investigators to insist that a primary malignant hepatic neoplasm could occur. In 1876 Kelsh and Kiener [4] reported 2 cases of primary carcinoma of the liver and found only 1 other case in the literature. In 1881 Sabourin [5] added

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We have included only the cases in which the primary carcinomatous growth could be localized definitely within the hepatic substance proper, as arising either from hepatic cells or from the small biliary capillaries. We have excluded any tumors arising from a hepatic duct, either external to the liver, at the porta hepatis or in the short course of this duct within the anatomic confines of the liver itself.[1] We believe that such tumors properly should be classified as "primary carcinomas of the hepatic duct."

1. Counseller, V. S., and McIndoe, A. H.: Primary Carcinoma of the Liver, Arch. Int. Med. **37**:363-387 (March) 1926.

2. McIndoe, A. H., and Counseller, V. S.: Primary Carcinoma of the Liver of Possible Multicentric Origin Occurring in a Case of Portal Cirrhosis, Am. J. Path. **2**:557-567 (Nov.) 1926.

3. Rokitansky, cited by Steiner.[15]

4. Kelsh, A., and Kiener, P. L.: Contribution a l'histoire de l'adénome du foie, Arch. de physiol. norm. et path. **3**:622-656, 1876.

5. Sabourin, C.: Contribution à l'étude des lésions du parenchyme hépatique dans la cirrhose; essai sur l'adénome du foie, Thesis, Paris, no. 39, 1881.

4 more cases. In 1888 Hanot and Gilbert[6] classified the tumors into three macroscopic groups: (1) *cancer nodulaire,* (2) *cancer massif* and (3) *cancer avec cirrhose.* They also suggested the microscopic distinction of *cancer trabéculaire* and *cancer alvéolaire.* In 1901, Eggel,[7] in an extensive and excellent review, collected 162 cases from the literature and added 1 of his own. He disagreed with Hanot and Gilbert's idea of a separate group of *cancer avec cirrhose,* for he noted that cirrhosis also may be found in the nodular and massive forms of carcinoma. Eggel's macroscopic classification still is acceptable: (1) multiple nodular form, (2) solitary massive form and (3) diffuse form. Histologically, Eggel divided the tumors into *carcinoma solidum* and *carcinoma adenomatosum.* In 1911 Goldzieher and von Bókay[8] suggested that the tumors which arise from hepatic cells be called *carcinoma hépatocellulaire* and that those which arise from the epithelium of the smaller bile ducts be known as *carcinoma cholangiocellulaire.* Yamigwa[9] later modified this nomenclature to "hepatoma" and "cholangioma," terms which are generally accepted today.

INCIDENCE

The present group of thirty-one tumors were detected in 16,303 necropsies at the Mayo Clinic, an incidence of 0.19 per cent. Twenty of the lesions were primary carcinomas of hepatic cells, or hepatomas; eleven were primary carcinomas of bile ducts, or cholangiomas.

RACE

We have collected from the literature 339 instances of a primary malignant process of the liver discovered in 159,144 necropsies among American and European peoples. This represents an incidence of 0.227 per cent, or about 1 instance in each 500 necropsies.

There seems to be little doubt that the disease is commoner among the Oriental peoples. A collected series of reports from Asiatic and African institutions revealed that 465 instances of primary carcinoma of the liver had been recorded in 47,292 necropsies. This represents a much higher incidence (0.983 per cent, or nearly 1 instance in each 100 necropsies) than that for European and American peoples.

6. Hanot, V. C., and Gilbert, A.: Études sur les maladies du foie; cancer (épithéliome); sarcome; mélanomes; ystes non parasitaires; angiomes, Paris, Asselin & Houzeau, 1888.

7. Eggel, H.: Ueber das primäre Carcinom der Leber, Beitr. z. path. Anat. u. z. allg. Path. **30**:506-604, 1901.

8. Goldzieher, M., and von Bókay, Z.: Der primäre Leberkrebs, Virchows Arch. f. path. Anat. **203**:75-131, 1911.

9. Yamigwa, K.: Zur Kenntnis des primären parenchymatösen Leberkarzinoms (Hepatoma), Virchows Arch. f. path. Anat. **206**:437-467, 1911.

Among 3,900 specimens obtained in South Africa, Pirie [10] found ninety-one carcinomas of all forms, of which thirty-six were primary carcinomas of the liver. He attributed the high incidence of the disease to the prevalence of schistosomiasis and associated hepatic damage among the natives. The parasite itself was found in 10 of the 36 cases.

Tull [11] has reported from Singapore the largest individual series in the literature—134 cases, of which 126 involved Chinese. The apparent prevalence of these tumors among the Chinese is thought to be due to the high incidence of liver fluke disease (infection with Clonorchis sinensis) in Kwantung, a province of southern China.

Boyce and McFetridge [12] reported that in 18 of their 28 cases the lesion had occurred in American Negroes. However, Lynch [13] observed no such increased incidence among Negroes in his report from Roper Hospital in Charleston, S. C., where the patients are almost exclusively Negroes.

TABLE 1.—*Incidence According to Age in Thirty-One Cases of Primary Carcinoma of the Liver*

| | Lesion | |
Age, Yr.	Hepatomas	Cholangiomas
1 to 9	1	..
10 to 19	..	..
20 to 29	1	..
30 to 39	..	1
40 to 49	3	3
50 to 59	6	4
60 to 69	7	2
70	2	1
Total	20	11

AGE

Primary carcinoma of the liver is a disease of older age groups; in 60.3 per cent of Eggel's cases the lesion afflicted persons from 41 to 70 years old. In our cases the average age for men was 58.5 years; for women, 48.9 years; for patients who died with hepatomas, 58.7 years, and for those who had cholangiomas, 56.9 years. The incidence according to age in our cases is shown in table 1.

10. Pirie, J. H. H.: Carcinoma of Liver in Natives and Its Frequent Association with Schistosomiasis, M. J. South Africa **17**:87 (Dec.) 1921.

11. Tull, J. C.: Primary Carcinoma of the Liver: A Study of One Hundred and Thirty-Four Cases, J. Path. & Bact. **35**:557-562 (July) 1932.

12. Boyce, F. F., and McFetridge, E. M.: Primary Carcinoma of the Liver: Report of Twenty-Eight Additional Cases, Internat. S. Digest. **18**:67-80 (Aug.) 1934.

13. Lynch, K. M.: Primary Liver Carcinoma: Relation to Yellow Atrophy Cirrhosis, South. M. J. **30**:1043-1049 (Nov.) 1937.

Primary cancer of the liver may occur among children; Noeggerath [14] reported a case in which the lesion was found in a newborn infant. Steiner [15] in 1938 accepted 75 cases from the literature, involving children, as being authentic. Tomlinson and Wolff [16] in 1942 added other reported cases to make a total of 82 authentic cases in which the lesion had afflicted children less than 16 years of age, as described in the literature to that date. In 1 of our cases, primary carcinoma of the hepatic cells attacked a girl 5 years old.

SEX

Primary carcinoma of the liver seems to be predominantly a disease of males. In almost two thirds of Eggel's cases the patients were males, whereas in 23 of our cases (74.2 per cent) the patients were males and only 8 (25.8 per cent) were females.

However, 57.1 per cent of the cancers of the bile ducts in Eggel's series occurred in women. Fried [17] has suggested that this increased tendency toward formation of cholangiomas in women may be caused by the prevalence of infection of the bile ducts followed by inflammatory hyperplasia of the smaller bile ducts. Six of the eleven cholangiomas but only two of the twenty hepatomas in the present series were found in women.

CAUSATION

There seems to be little doubt that chronic irritation of the liver is a prominent causative feature. Twenty-nine of Tull's patients had syphilis, and 6 had malaria. Sanes and MacCallum [18] have reported 2 cases in which cholangioma was associated with hepatolithiasis, cholangitis and cholestasis. Four of our patients drank excessively, 3 had syphilis and 4 were known to have had malaria or typhoid fever. Yamigwa [9] and Ewing [19] suspected that tumors such as those under consideration might arise from embryonic cell rests, but this suspicion never has been confirmed.

14. Noeggerath, E., cited by Steiner.[15]

15. Steiner, M. M.: Primary Carcinoma of the Liver in Childhood: Report of Two Cases with a Critical Review of the Literature, Am. J. Dis. Child. **55**:807-824 (April) 1938.

16. Tomlinson, W. J., and Wolff, E.: Primary Liver-Cell Carcinoma in Infancy: Report of Two Cases, One Showing Calcification, Am. J. Clin. Path. **12**:321-327 (June) 1942.

17. Fried, B. M.: Primary Carcinoma of the Liver, Am. J. M. Sc. **168**:241-267 (Aug.) 1924.

18. Sanes, S., and MacCallum, J. D.: Primary Carcinoma of the Liver: Cholangioma in Hepatolithiasis, Am. J. Path. **18**:675-687 (July) 1942.

19. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 738-753.

PARASITIC INFECTION

Practically all authors from the Orient and Africa stress the causative role of parasitic infection, especially by the liver fluke Clonorchis sinensis and the blood flukes Schistosoma mansoni and Schistosoma japonicum. These parasites are known to damage the liver, and it is believed that this hepatic irritation serves as a precursor for the development of the primary malignant hepatic disease. In a recent publication, however, Hartz [20] wrote that he did not regard schistosomiasis as playing a significant role in the causation of cancer of the hepatic cells in the Chinese.

CIRRHOSIS

A high incidence of cirrhosis accompanying primary carcinoma of the liver has been noted for some time, a coincidence which is unusual when the liver is the seat of metastatic carcinoma. Of 1,989 cases of cirrhosis collected from the literature, Berk and Lieber [21] found 90 (4.5 per cent) in which the condition was associated with primary cancer of the liver.

In the presence of cirrhosis, as in all chronic destructive processes in the liver, there is constant demand for repair. In fact, degeneration, fibrosis, condensation in the bile duct and evidence of regeneration form the cardinal pathologic signs of cirrhosis. Many times this regeneration amounts to an overgrowth, an actual hyperplasia. Eventually, this compensatory hypertrophy may give rise to the formation of multiple hyperplastic nodules, some of which, it is thought, might proceed to become malignant. Of course, what causes one regenerative nodule to remain benign and the other to become malignant is not known. Distinction between the regenerative hyperplasia in certain benign conditions (that is, the "primary toxic necrosis" in case 2 of Wilbur, Wood and Willett [22]) and that which occurs in malignant conditions often is exceedingly difficult. In figure 1 *a* is shown what we consider to be a regenerative hyperplastic nodule of cirrhosis. The decided proliferation, with multinucleated large cells, is apparent and might easily be mistaken for an early primary carcinoma of the hepatic cells.

Because of the extensive vascular growth of the tumor under consideration, pressure atrophy, necrosis and fibrosis adjacent to the tumor often occur. This localized process is unassociated with any diffuse regeneration and must be distinguished from a cirrhotic process.

20. Hartz, P. H.: Role of Schistosomiasis in the Etiology of Cancer of the Liver in the Chinese, Arch. Path. **39**:1-3 (Jan.) 1945.

21. Berk, J. E., and Lieber, M. M.: Primary Carcinoma of the Liver in Hemo-Chromatosis, Am. J. M. Sc. **202**:708-714 (Nov.) 1941.

22. Wilbur, D. L.; Wood, D. A., and Willett, F. M.: Primary Carcinoma of the Liver, Ann. Int. Med. **20**:453-485 (March) 1944.

In a collected series reported in the literature, in 74.1 per cent of 351 cases hepatoma was associated with cirrhosis, whereas in 131 cases of cholangiomas collected by the same authors only 52.7 per cent of
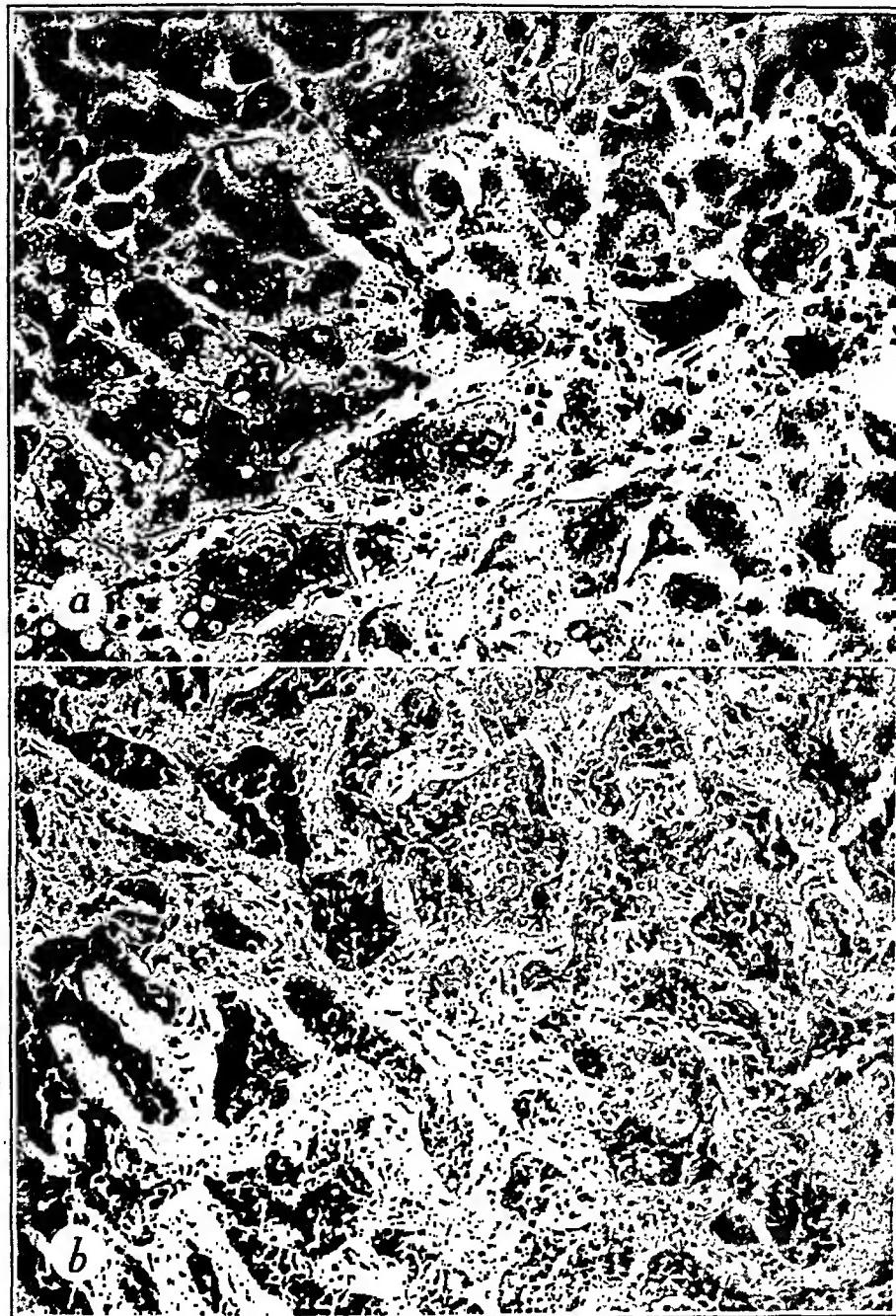
Fig. 1.—(*a*) Histologic section of a nodule from cirrhosis of the liver, showing regenerative hyperplasia and large hepatic cells, many of which are multinucleated. Hematoxylin and eosin. × 200. (*b*) Histologic section of tumorous tissue in case 1, showing the bile duct arrangement of the cells and the abundant connective tissue stroma which are typical of carcinoma of the cells of the bile duct (cholangioma). Hematoxylin and eosin. × 145.

the tumors occurred in association with cirrhosis. In our cases, fifteen of the twenty hepatomas (75 per cent) but only two of the eleven cholangiomas (18.2 per cent) were found in cirrhotic livers.

HEMOCHROMATOSIS

Rowen and Mallory[23] were among the first to suggest that so-called pigmentary cirrhosis might afford an even greater possibility for the development of primary carcinoma than do the other types of cirrhosis.

Sheldon,[24] in his excellent monograph on the subject in 1935, found that in 7.1 per cent of all accepted cases of hemochromatosis in the literature the condition was associated with primary carcinoma of the liver, and he concluded that there is no greater incidence of primary malignant growth of the liver in pigmentary cirrhosis than in nonpigmentary cirrhosis.

Recently, however, Binford, Lawrence and Wollenweber[25] again reviewed the literature and found that twenty-nine primary carcinomas of the liver had occurred in 387 cases of hemochromatosis, an incidence of 7.5 per cent. When Berk and Lieber in 1941 found only ninety primary malignant processes of the liver in 1,989 cases of cirrhosis collected from the literature, they again raised the question of whether hemochromatosis might not be complicated by primary · carcinomatous change more frequently than other types of cirrhosis. We shall not attempt to settle the argument. In 1 of our cases, carcinoma of the liver was associated with hemochromatosis.

DIET

Recent experimental work[26] has been done by which it is shown that damage to the liver, cirrhosis and primary cancers can be produced in rats by the feeding of the substance butter yellow, or dimethylaminoazobenzene. Investigators[27] have found that the feeding of rats on diets rich in protein or the amino acids, cystine and choline, together with the vitamin B complex and especially riboflavin, would protect the livers against the formation of tumor. Additional studies are indicated in this regard.

23. Rowen, H. S., and Mallory, F. B.: A Multinucleated Liver Cell Carcinoma, Am. J. Path. **1**:677-680 (Nov.) 1925.

24. Sheldon, J. H.: Haemochromatosis, London, Oxford University Press, 1935.

25. Binford, C. H.; Lawrence, R. L., and Wollenweber, H. L.: Hemochromatosis with Primary Carcinoma of the Liver, Arch. Path. **25**:527-533 (April) 1938.

26. Kinosita, R.: Studies on Cancerogenic Chemical Substances, Tr. Soc. path. jap. **27**:665-725, 1937.

27. György, P.; Poling, C. E., and Goldblatt, H.: Necrosis, Cirrhosis and Cancer of Liver in Rats Fed Diet Containing Dimethylaminoazobenzene, Proc. Soc. Exper. Biol. & Med. **47**:41-44 (May) 1941. Miller, J. A.; Miner, D. L.; Rusch, H. P., and Baumann, C. A.: Diet and Hepatic Tumor Formation, Cancer Research **1**:699-708 (Sept.) 1941.

TRAUMA

In a few cases [28] primary carcinoma seems to have been precipitated by an abdominal injury, but development of the malignant lesion may have been purely coincidental.

CLINICAL FEATURES

A review of our own cases and of those in the literature reveals no signs or symptoms pathognomonic to this disease. Ewing has suggested four well defined clinical groups: (1) that in which no symptoms are detected and the patient dies suddenly from hemorrhage or after an illness of a few days, as noted by Karsner [29]; (2) that in which latent carcinoma is found among patients who succumb to cirrhosis or other diseases; (3) that in which the usual history of cirrhosis terminates rapidly with hepatic tumor, jaundice, ascites and cachexia, and (4) that in which the usual history of a malignant tumor, indicating from the first involvement of the liver, develops among previously healthy patients.

The diagnosis is rarely made before the death of the patient. In 1 of our cases the clinical possibility of a primary carcinoma of the liver was entertained. In 8 other cases, the results of biopsy of the liver at the time of surgical exploration were considered to be positive for malignant growth and indicative of primary carcinoma of the liver.

In 27 of our cases (87.1 per cent) and a similarly high percentage of those in the literature, the patients have suffered from weakness and rapid loss of weight. One of our patients, however, had noted a definite gain of weight, which was probably the result of pronounced anasarca throughout the body. Twenty-four of our patients (77.4 per cent) were found to have ascites at necropsy, and in 7 of these patients the ascitic fluid was blood tinged or bloody. The ascites may have resulted from portal obstruction or from metastasis to the peritoneum. Associated edema of the ankles was observed among 23 patients. Twenty-seven of our patients (87.1 per cent) complained of some type of abdominal pain, which varied from minimal distress to severity requiring opiates for relief. Eight of these patients had associated pain in the back, and 6 had pain in the shoulder. Fourteen of our patients (45.2 per cent) had noted nausea and vomiting. Four of these patients had minor bouts of hematemesis, but for none was it a fatal complication. Since a high percentage of the malignant processes in question occur in cirrhotic livers, it might be expected that an occasional patient would die from a ruptured esophageal varix. Only 3 of our patients had specifically complained of diarrhea, and most of them had become increas-

28. Crawford, W. H.: Hypoglycemia with Coma in Case of Primary Carcinoma of the Liver, Am. J. M. Sc. **181**:496-502 (April) 1931.

29. Karsner, H. T.: A Clinicopathological Study of Primary Carcinoma of the Liver, Arch. Int. Med. **8**:238-261 (Aug.) 1911.

ingly constipated. Eighteen of our patients (58.1 per cent) were jaundiced. Jaundice often was mild or moderate, the highest value for serum bilirubin content in our series being 21.7 mg. per hundred cubic centimeters of serum. The van den Bergh reaction frequently is direct, particularly in the higher readings. Tull commented, "It is remarkable that one so often sees a liver actually riddled with new growth, and yet no jaundice." The spleen was palpable in only 6 of our cases (19.4 per cent). Necropsy, however, revealed the spleen to weigh in excess of 300 Gm. in 18 of our 31 cases. That this splenic enlargement is not palpable more frequently may well be due to the commonly associated abdominal distention and ascites. The high incidence of splenomegaly probably is associated with the frequent occurrence of cirrhosis in these cases, but Karsner expressed the opinion that toxemia also may be a factor. Eight patients (25.8 per cent)

TABLE 2.—*Signs and Symptoms in Thirty-One Cases of Primary Carcinoma of the Liver, as Compared with Those in Reports from the Literature*

Sign or Symptom	Percentages According to Series Reported			
	Mayo Clinic	Eggel's [7]	Tull's [11]	Greene [*]
Weakness	87.1	....	88.8	..
Rapid loss of weight	71	....	....	41
Abdominal distention	87.1	....	....	..
Ascites	77.4	58.5	47	68
Abdominal pain	87.1	....	8.9	29
Nausea and vomiting	45.2	....	2.2	..
Edema of the ankles	74.2	41	84.3	15
Jaundice	58.1	61	34.3	52
Palpable spleen	19.4	32	38.9	34
Dilated superficial abdominal veins	25.8	....	52.2	..
Fever	38.7	14	27.6	..
Palpable abdominal mass	58.1	....	67.9	..

[*] Greene, J. M.: Internat. Abstr. Surg. 69:231, 1939.

had decidedly dilated superficial abdominal veins, a condition which is thought also to be due to the cirrhosis and the attendant portal obstruction. Fever was found in 12 cases (38.7 per cent) and often was a terminal condition. White [30] regarded fever as an exceedingly prominent and suggestive symptom of primary carcinoma of the liver. Wilbur, Wood and Willett, on the other hand, recently reported a case in which hypothermia was consistent and pronounced.

Progressive enlargement of the liver is perhaps the outstanding physical sign. An abdominal mass was palpated in 18 of our 31 cases (58.1 per cent), and in 6 others the liver was enlarged without a definitely palpable tumor. In the other 7 cases the liver was not enlarged, and in 4 of these it was even decreased in size. The largest liver in our series weighed 6,260 Gm. On the basis of the data in table 2 it is apparent that the outstanding signs and symptoms in our cases were

30. White, W. H.: Primary Carcinoma of the Liver, in Allbutt, T. C., and Rolleston, H. D.: A System of Medicine, London, Macmillan & Company, Ltd., 1908, vol. 4, pt. 1, pp. 215-222.

emaciation, abdominal distention with ascites, abdominal pain, edema of the ankles, jaundice and a palpable abdominal tumor.

Nadler and Wolfer [31] were the first to report a case in which spontaneous hypoglycemia had been caused by primary carcinoma of the liver. Crawford [28] and Beers and Morton [32] have since reported similar cases. The pancreas in each case was grossly and microscopically normal. Spontaneous rupture of the liver at the carcinomatous site has been reported as a terminal complication by several authors,[33] but we encountered no such complications.

The laboratory was of little assistance in diagnosis of the condition in these cases. Thirteen patients had varying degrees of anemia, and 7 had leukocytosis ranging in severity up to 26,000 leukocytes per hundred cubic centimeters of blood. Some degree of uremia was present in 11 cases, but this occasionally was only a terminal complication. Tests of hepatic function will indicate hepatic disturbance but not particularly a malignant process. Cunningham [34] has said that elevation of the value for the alkaline phosphatase content of the serum may be especially significant in primary carcinoma of the liver. This test had not been carried out for any of our patients.

Brulé [35] has suggested that fixity of the liver may be an important diagnostic point, and Strong and Pitts [36] expressed the belief that upward movement of the liver, resulting from the fact that the resistance presented by ascites is greater than that of the diaphragm, may be significant. In the present series none of these observations could be made consistently. Mallory's patient (no. 22051)[37] underwent an exploratory operation for suspected mediastinal tumor, which was found to be actually a primary hepatoma pushing the diaphragm high into the

31. Nadler, W. H., and Wolfer, J. A.: Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, Arch. Int. Med. **44**:700-710 (Nov.) 1929.

32. Beers, D. N., and Morton, J. J.: Primary Carcinoma of the Liver with Hypoglycemia, Am. J. Cancer **24**:51-55 (May) 1935.

33. Mast, W. H., and Streamer, C. W.: Primary Carcinoma of the Liver with Spontaneous Rupture, J. A. M. A. **100**:1684 (May 27) 1933. Schnabel, T. G.: Primary Carcinoma of the Liver with Spontaneous Rupture and Lethal Hemorrhage, Ann. Surg. **101**:613-616 (Jan.) 1935. Jenks, A. L.; Powell, L. D., and Kaump, D. H.: Primary Carcinoma of the Liver with Spontaneous Rupture, J. Iowa M. Soc. **29**:193-197 (May) 1939.

34. Cunningham, R. M.: Primary Carcinoma of the Liver: A Clinical-Pathologic Report of Fourteen Cases at University Hospital from 1927 to 1943, Bull. School Med. Univ. Maryland **28**:61-79 (Oct.) 1943.

35. Brulé, M., cited by Counseller and McIndoe.[1]

36. Strong, G. F., and Pitts, H. H.: Primary Carcinoma of the Liver, Arch. Int. Med. **46**:105-120 (July) 1930; Further Observations on Primary Carcinoma of the Liver in Chinese, Ann. Int. Med. **6**:485-496 (Oct.) 1932.

37. Primary Cancer of Liver, Hepatoma, Cabot Case 22051, New England J. Med. **214**:209-211 (Jan. 30) 1936.

thorax.   One of our patients was believed, clinically, to have bron-
chogenic carcinoma of the lower lobe of the right lung, which was found
at necropsy to be extensive pulmonary infarction associated with pul-
monary metastasis from a relatively small primary carcinoma of the
bile duct.

In summary, we may say that diagnosis of primary carcinoma of
the liver in a living person is exceedingly difficult, at best.   There
are no pathognomonic symptoms, physical signs or decisive observa-
tions which can be made in the laboratory or roentgenologically.
Biopsy of hepatic tissue offers the best chance for antemortem diagnosis,
but many of the patients are in such poor general condition that even
this simple procedure is attended with risk.

PATHOLOGIC DATA

Before the diagnosis of primary carcinoma of the liver can be made,
it is imperative to search carefully, both grossly and microscopically,
for a primary focus.   Particular attention in this regard should be
paid to the adrenal bodies, kidneys, breasts and gastrointestinal tract.
Since the histologic picture of cholangioma resembles so closely that of
carcinoma of the extrahepatic bile ducts, the biliary tree and gallbladder
must be excluded as a primary focus in all cases.

The proportion of occurrence of primary to secondary carcinoma
of the liver has been variously given as 1 : 64.5 by Hansemann,[38] 1 : 44
by Counsellor and McIndoe and 1 : 13.5 by Lisa and Hart.[39]   There
are no reliable features which will distinguish the two types of car-
cinoma grossly, although umbilication probably is seen oftener in the
metastatic processes than in the primary lesions.

MACROSCOPIC FEATURES

Hanot and Gilbert[6] originally expressed the opinion that it was
possible to distinguish clinically between carcinoma of the hepatic cells
and carcinoma of the bile duct.   Eggel[7] and Karsner[29] did not believe
that this was consistently possible.   In fact, gross distinction between
the two types of carcinoma at necropsy usually is extremely difficult.
Ewing has suggested that extensive hemorrhage, necrosis, bulky soft
tumorous masses and prominent invasion of the large veins are more
likely to occur in the presence of hepatoma but that none of these is
pathognomonic.

Eggel described three groupings based on macroscopic appearance,
which still may be used: (1) a solitary massive group, in which one

38. Hansemann, D.:   Ueber den primären Krebs der Leber, Berl. klin.
Wchnschr. **27**:353-356 (April 21) 1890.

39. Lisa, J. R., and Hart, J. F.: Primary Carcinoma of the Liver, New York
State J. Med. **38**:1537-1542 (Dec. 15) 1938.

massive nodule may occupy an entire lobe, with numerous smaller tumorous nodules in the adjacent hepatic tissue, (2) a multiple nodular group, in which there are many discrete nodules, varying from a few millimeters to several centimeters, and (3) a diffuse group, in which the entire substance of the liver contains tumorous nodules the size of acini, surrounded by a strong framework of connective tissue. Distinction of the last type from cirrhosis often is possible only with the aid of the microscope.

In 23 per cent of Eggel's cases the lesions were of the massive type, in 64.6 per cent the lesions were multiple nodular and in 12.4 per cent the process was diffuse. In 11 of our cases (35.5 per cent) we found massive tumorous nodules, and in 20 (64.5 per cent) the lesions were classified as "multiple nodular." We had no lesions of the diffuse type, since some degree of nodularity was always apparent.

Ewing and Rolleston and McNee[40] mentioned the frequency with which the primary tumor arises in the right lobe of the liver. In our 11 cases in which massive nodules were present, nine tumors arose in the right lobe, one tumor arose in the left lobe and one arose in the middle of the liver. In the group of multiple nodular lesions, the tumorous masses were present to about equal degree in both lobes.

Ewing has included in his anatomic classification "solitary adenoma or solitary hepatoma." This rare, clinically benign, encapsulated tumor of the liver, which has a varying degree of cellular activity, apparently owes its benignity to its encapsulation. We have no such tumors in this series.

We do not include herein any so-called adenomas of the bile duct, which are small benign malformations of the bile ducts seen not infrequently at necropsy.

Jaffe[41] in 1924 mentioned the fact that 48 cases of primary sarcoma of the liver had been reported previously, in only 29 per cent of which cirrhosis was present. We found no such cases.

The literature contains more reports of hepatomas than reports of cholangiomas, the proportion in our collected series being nearly 3:1 in favor of hepatomas. Wu and Kang[42] suggested that this preponderance of hepatomas may be due to a more active regeneration of hepatic cells than of cells of the bile duct.

Four important features distinguish between hepatoma and cholangioma microscopically (figs. 1 *b*, 2 and 3). These features will be considered next.

40. Rolleston, H., and McNee, J. W.: Diseases of the Liver, Gall-Bladder and Bile-Ducts, ed. 3, London, Macmillan & Company, Ltd., 1929, pp. 489-504.

41. Jaffe, R. H.: Sarcoma and Carcinoma of the Liver Following Cirrhosis, Arch. Int. Med. **33**:330-342 (March) 1924.

42. Wu, C. J., and Kang, H. J.: Primary Carcinoma of the Liver, Nat. M. J. China **16**:234-243 (April-June) 1930.

Arrangement of the Cells.—The tumors tend to conform to the structure of the tissue from which they arose. Cancers of the hepatic cells are arranged in cords and may even simulate lobules of hepatic tissue. Rosette-like structures may be seen. Cancers of the bile duct form tubuloalveolar structures (fig 1 *b*) which oftener possess lumens than do tumors of hepatic cells.
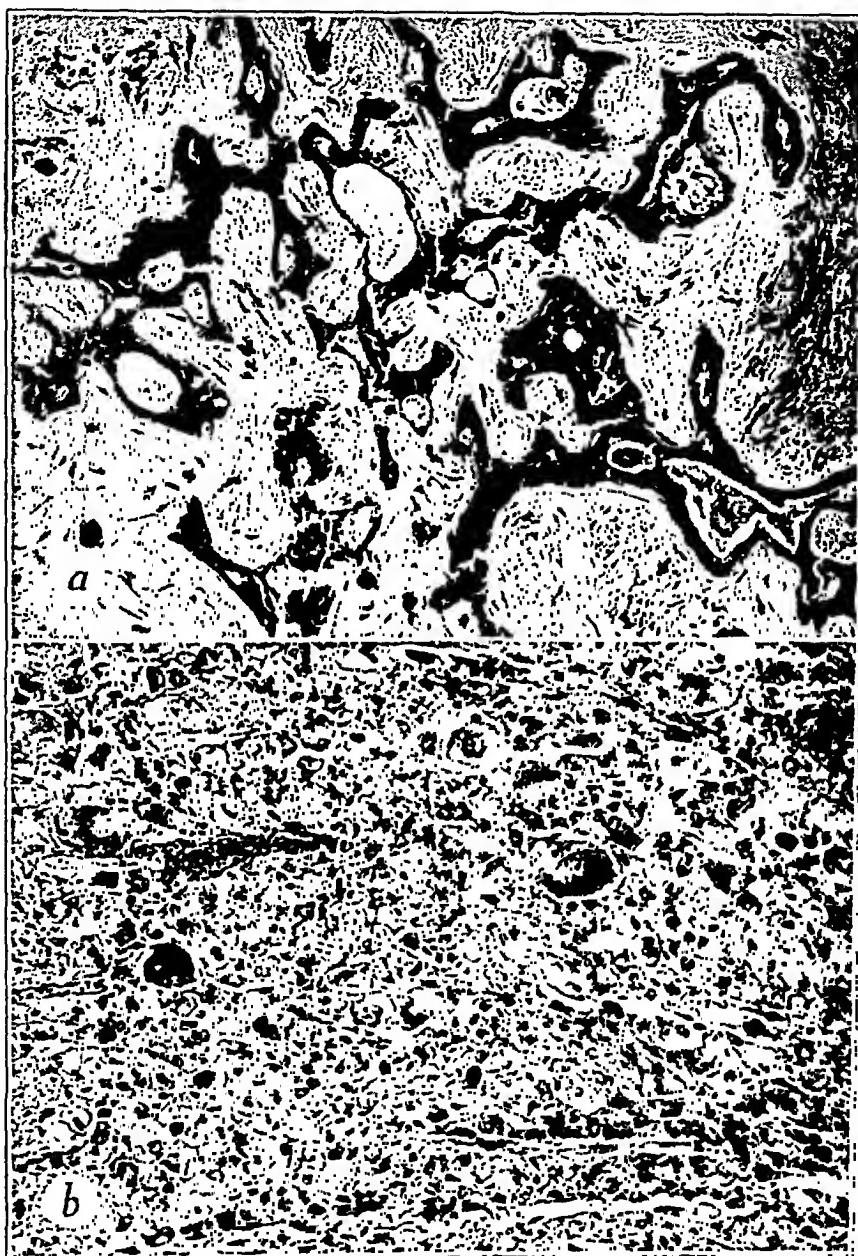
Fig. 2.—(*a*) Histologic section of cholangioma of the liver, showing an increase in fibrous tissue and the arrangement of the tumorous cells simulating bile ducts, with lumens containing hyaline material and cellular debris. Hematoxylin and eosin. × 145. (*b*) Histologic section of the tumorous tissue in case 2, showing the similarity of the tumorous cells to hepatic cells and their arrangement, together with the thin capillary stroma, all of which are the diagnostic criteria of the carcinoma of the hepatic cells (hepatoma). Hematoxylin and eosin. × 145.

Type of the Cells.—The hepatomatous cell is polygonal and poly-hedral, with a granular, usually acidophilic cytoplasm which occasionally contains bile. There are large, round, vesicular nuclei which often contain multiple nucleoli. Multinucleated giant cells and atypical bizarre mitosis may be seen (figs. 2 *b* and 3 *b*), and areas of necrosis occur frequently. The cholangiomatous cell is cuboid or cylindric, with a clear, somewhat basophilic cytoplasm. The nuclei usually are small and hyperchromatic. Giant cells, multiple nucleoli and bizarre types of mitosis infrequently are seen. Most of the tumors in either group would be classified grade 3 or 4 on the basis of Broders'[43] grading, although the hepatomas at first consideration seem to be more active because of the giant cells and bizarre types of mitosis.

Type of Stroma.—The type of stroma is one of the most reliable differential points in cases in which the decision is questionable. The cancer of the hepatic cells has a capillary stroma, whereas the cancer of the bile duct has a connective tissue stroma, with a strong tendency toward cicatricial contraction of the tumorous nodules. This frame-work of fibrous tissue may be well illustrated by special stains for con-nective tissue. Either type of lesion may possess a moderate lymphocytic reaction in the stroma, especially if cirrhosis is associated.

Secretion of Bile.—Either type of tumor may be stained deep green by the generalized jaundice and microscopically may exhibit inspissated bile or bile thrombi in the lumens. However, the intracellular existence of bile pigment is considered to be an inherent characteristic of the hepatic cell alone and was thought by Ribbert[44] to be of importance in differential diagnosis. Eggel found intracellular bile pigment in 15 of his 163 cases, and, of these, in 3 there was bile in the metastatic processes. Fox and Bartels,[45] in their study of 80 cases, found bile pigment in fifteen of the primary tumors and in four of the metastatic processes. In our 20 cases of hepatoma, we discovered intracellular bile pigment in 5 cases, in 1 of these the metastatic process, but we did not find it in any of the cases of cholangioma.

Gustafson[46] has reported 2 cases in which neoplastic lesions of both bile duct and parenchymal hepatic cells had occurred, and Pirie found

43. Broders, A. C.: Squamous-Cell Epithelioma of the Lip: A Study of Five Hundred and Thirty-Seven Cases, J. A. M. A. **74**:656-664 (March 6) 1920.

44. Ribbert, H.: Das maligne Adenom der Leber, Deutsche med. Wchnschr. **2**: 1607-1609 (Sept.) 1909.

45. Fox, R. A., and Bartels, G. W.: Primary Carcinoma of the Liver: Report of Three Cases, Arch. Path. **6**:228-239 (Aug.) 1928.

46. Gustafson, E. G.: An Analysis of Sixty-Two Cases of Primary Carcinoma of the Liver Based on 24,400 Necropsies at Bellevue Hospital. Ann. Int. Med. **11**:889-900 (Dec.) 1937.

five such mixed tumors in his 36 cases.　Warvi [47] has suggested "cholangiohepatoma" as the best name for this rare condition.　It is important that the condensation in the bile duct which accompanies
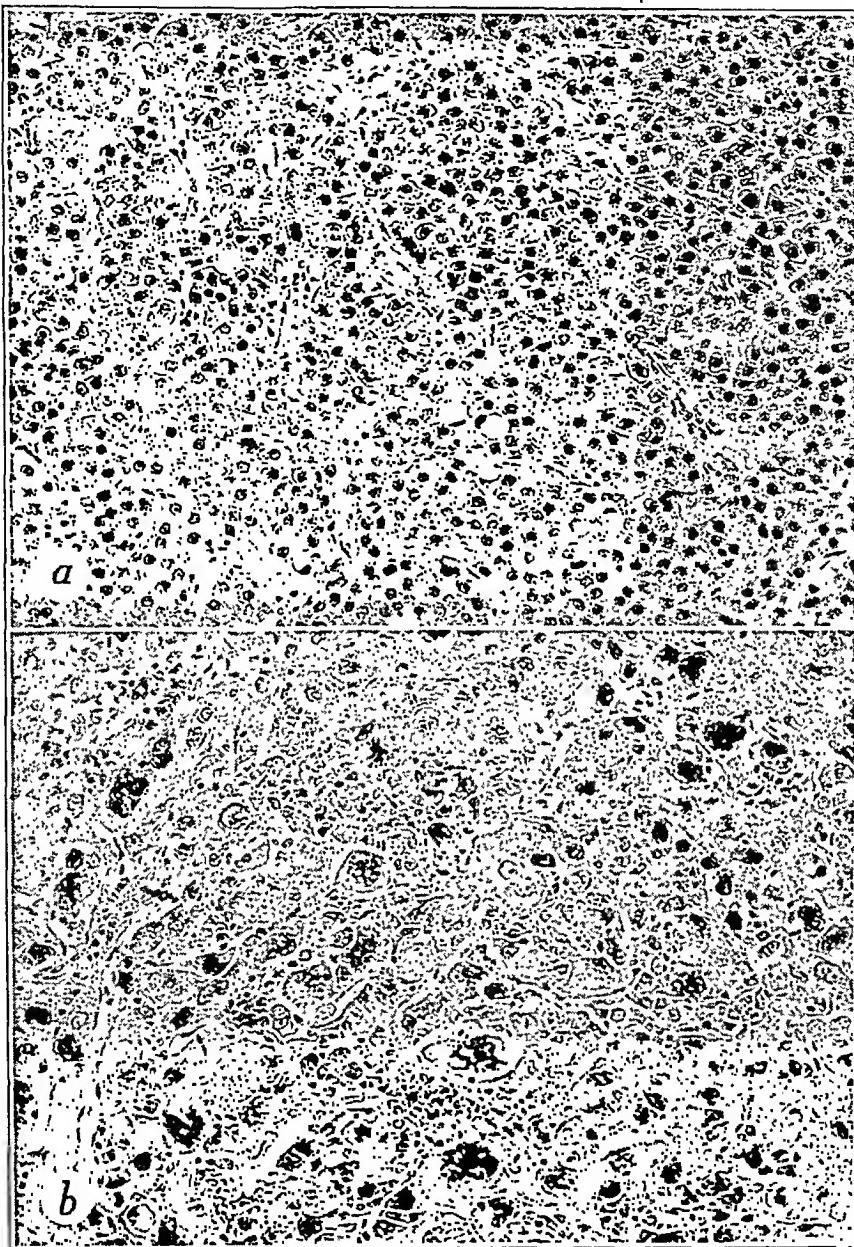
Fig. 3.—(*a*) Histologic section of tissue from a hepatoma; the tumorous cells have a cordlike arrangement, and the capillary stroma is fine.　The malignant part of this tumor is much lower than that of the hepatomas seen in figures 2*b* and 3*b;* yet decided destruction of hepatic tissue has occurred.　Intracellular bile pigment was seen in parts of this tumor.　Hematoxylin and eosin. × 145.　(*b*) Histologic section of a hepatoma, showing the resemblance of the tumorous cells to hepatic cells and the fine capillary stroma.　Hematoxylin and eosin.　× 170.

47. Warvi, W. N.: Primary Neoplasms of the Liver, Arch. Path. **37:**367-382 (June) 1944.

cirrhosis not be considered to be the cholangiomatous portion of this mixed tumor.

MULTICENTRIC VERSUS UNICENTRIC ORIGIN

The question of whether the origin of these tumors is multicentric or unicentric has been argued for years. Goldzieher and von Bókay supported the former view when they could find no direct continuity from one neoplasm to another in careful study of serial sections. Ribbert and, later, Winternitz [48] favored the latter view and stated the belief that the tumor spread intrahepatically from its unicentric origin by way of its early invasion of the portal system. A majority of authors now seem to believe, with Loesch, [49] that most of these tumors arise unicentrically, although multicentric origin may occur rarely in some cirrhotic livers. One of our cases was previously reported by McIndoe and Counseller [2] as an example of possible multicentric origin of the tumors.

EXTENSION

The secondary spread of primary carcinoma of the liver takes place by direct extension and by metastasis through the blood and lymph channels. The hepatomatous cells early invade the smaller radicles of the portal vein, thus causing rapid dissemination of the malignant nodules throughout the liver. The hepatomatous cells may grossly invade the efferent veins from the liver as well (fig. 4). Eggel found tumorous thrombosis in the large veins in 35 of his 163 cases. Simpson [50] in 1924 studied 78 cases of tumorous thrombosis of the inferior vena cava and found that in 7 (10 per cent) cases the condition had been caused by primary carcinoma of the liver.

Gregory [51] in 1939 studied 12 cases of primary carcinoma of the liver with tumorous thrombosis of the inferior vena cava. The two outstanding physical manifestations, he noted, were swelling of the patients' lower extremities and ascites. The tumorous thrombosis may extend into the right auricle and thereby cause symptoms of cardiac failure. Small pulmonary emboli from these thrombotic processes may be observed microscopically.

In no cases of cholangioma was there invasion of blood vessels. In 8 of the 20 cases of hepatoma, the tumor had invaded only the smaller branches of the portal and hepatic veins, but in 2 of these tumorous

48. Winternitz, M. C.: Primary Carcinoma of the Liver, Johns Hopkins Hosp. Rep. **17**:143-184, 1916.

49. Loesch, J.: Primary Carcinoma of the Liver, Arch. Path. **28**:223-235 (Aug.) 1939.

50. Simpson, W. M.: Tumor-Thrombosis of Inferior Vena Cava, with Four Additional Cases of Neoplastic Invasion, Ann. Clin. Med. **3**:29-68 (July) 1924.

51. Gregory, R.: Primary Carcinoma of the Liver: Tumor Thrombosis of the Inferior Vena Cava and Right Auricle, Arch. Int. Med. **64**:566-578 (Sept.) 1939.

emboli were found microscopically in the lungs. In 2 other cases tumorous thrombosis of the portal and hepatic veins had extended into the inferior vena cava and right auricle. In another case (case 2) tumorous thrombosis of the hepatic vein and inferior vena cava was complicated by retrograde thrombosis of the left renal vein and by uremia.

Ewing mentioned the fact that extrahepatic metastasis is seen earlier and more frequently in cancers arising from the small bile ducts than

Fig. 4.—Large tumorous thrombosis of the hepatic vein and inferior vena cava in case 2.

in those arising from the hepatic cells. This discrepancy is hard to explain when the much more prominent invasion of blood vessels by hepatomas is considered. We found extrahepatic metastasis to be present in 21 of our 31 cases (67.7 per cent). However, in only 11 of our 20 cases of hepatoma (55 per cent) was there distal metastasis, whereas in 10 of our 11 cases of cholangioma (91 per cent) there was distal metastasis, facts which tend to support Ewing's impression. It is apparent, on the basis of table 3, that distal metastasis in our cases occurred most frequently in the regional lymph nodes and the lungs.

Charache,[52] in his review of the literature in 1939, found 18 cases in which skeletal metastásis had occurred, an incidence of 1.6 per cent of all cases of primary carcinoma of the liver. In 3 of our cases bony metastasis had occurred, and in each case the metastatic process was situated in the spinal column.

PROGNOSIS AND TREATMENT

The tumors under consideration grow exceedingly rapidly. Most of the patients die within a few months after the onset of the symptoms. The only possible treatment is surgical resection of the liver, which is performed with great risk and oftenest unsuccessfully. Keen[53] in 1899

TABLE 3.—*Sites of Sixty-One Extrahepatic Metastatic Processes in Thirty-One Cases of Primary Carcinoma of the Liver*

Metastatic Process, Site	Type of Tumor		
	Hepatic Cell (20 Cases)	Bile Duct Cell (11 Cases)	Total
Periportal lymph nodes	6	8	14
Lung	9	4	13
Mediastinal lymph nodes	3	3	6
Peritoneum	1	2	3
Diaphragm	2	2	4
Omentum	2	1	3
Stomach (by direct extension)	0	1	1
Duodenum (by direct extension)	1	0	1
Gallbladder (by direct extension)	0	2	2
Pancreas	1	2	3
Spleen	0	2	2
Adrenal glands	2	3	5
Ureter	0	1	1
Vertebra	1	2	3
Sites, total	28	33	61

collected 76 cases in which the liver had been resected for a neoplastic condition, with an immediate fatality rate of 14.9 per cent. Yeomans[54] in 1915 reported a second unsuccessful operation for recurrent primary carcinoma of the liver, the original tumor of which had been successfully removed, first, seven years before. Wallace[55] in 1941 collected 29 cases of "removable hepatoma" from the literature and added a case

52. Charache, H.: Primary Carcinoma of the Liver: Report of a Case and Review of the Literature, Am. J. Surg. **43**:96-105 (Jan.) 1939.

53. Keen, W. W.: Report of a Case of Resection of the Liver for the Removal of a Neoplasm, with a Table of Seventy-Six Cases of Resection of the Liver for Hepatic Tumors, Ann. Surg. **30**:267-283 (Sept.) 1899.

54. Yeomans, F. C.: Primary Carcinoma of the Liver, with Report of a Patient Who Remained Well Over Two Years After Operation, J. A. M. A. **52**:1741-1743 (May 29) 1909; Primary Carcinoma of the Liver: Operation for Recurrence Over Seven Years After Primary Operation, ibid. **64**:1301-1303 (April 17) 1915.

55. Wallace, R. H.: Resection of Liver for Hepatoma, Arch. Surg. **43**:14-20 (July) 1941.

of his own. Most authors agree with Yeomans that "the only hope for improvement in results lies in the direction of earlier operative exploration in patients with tumors in the right upper quadrant in whom no primary growth can be found elsewhere in the abdomen."

REPORT OF CASES

CASE 1.—A man 59 years old was admitted to the clinic on Dec. 26, 1931 because of sharp pain in the lower part of the thorax on the right side. This pain was aggravated by breathing. It had been present for three weeks. The patient had used alcohol excessively until three years before the time of his registration. Results of a general physical examination at this time were essentially normal. Results of urinalysis and blood cell counts were normal. Roentgenograms of the thorax and roentgenoscopic examination of the stomach disclosed nothing significant. A cholecystogram revealed a "poorly functioning gallbladder." The patient's pain increased in severity, and he lost 20 pounds (9 Kg.) in the next three weeks. A sulfobromophthalein excretion test of hepatic function revealed retention of dye, grade 4. The serum bilirubin content measured 1.2 mg. per hundred cubic centimeters of serum and gave the indirect van den Bergh reaction. The liver rapidly increased in size and felt nodular and extremely hard. Ascites became increasingly evident. A second roentgenogram of the thorax was reported as showing "infiltration of the right base and a small amount of fluid in the right base." Another leukocyte count amounted to 17,400 per cubic millimeter of blood. The value for blood urea was 32 mg. per hundred cubic centimeters of blood. The patient failed rapidly, and he died three months after registration. The clinical diagnosis was cirrhosis, metastatic malignant growth of the liver or possible primary cancer of the liver after long-standing cirrhosis.

Necropsy was performed two hours after death of this patient. The report was primary carcinoma of the liver with metastasis to the spleen and the lymph nodes; edema of the lungs with bronchopneumonia; ascites and bilateral hydrothorax; hemorrhage occurring into the wall of the stomach; cholelithiasis (eleven stones); hypertrophy of the prostate gland, grade 2; two diverticula of the urinary bladder; healed tuberculosis of the hilar lymph nodes, and arteriosclerosis of grade 2.

The skin was jaundiced to grade 1, and edema of the legs, grade 1, was noticed. The peritoneal cavity contained 2,500 cc. of turbid brownish fluid, but there were no signs of peritonitis. There was about 100 cc. of straw-colored fluid in each pleural cavity. The spleen weighed 298 Gm.; on the cut surface were seen many firm white-yellow nodules up to 0.3 cm. in diameter. The gallbladder contained 50 cc. of thick tarry bile and eleven small mulberry stones. The mucosa exhibited cholesterosis of grade 1. The extrahepatic bile ducts, pancreas and duodenum appeared to be normal. The lesser curvature of the stomach was firmly attached to the liver. The stomach contained 150 cc. of reddish brown fluid, and the mucous membrane was diffusely congested. Along the lesser curvature of the stomach were several enlarged firm lymph nodes which appeared to contain metastatic carcinoma. The liver weighed 3,782 Gm. and was covered with rough whitish nodules up to 5 cm. in diameter (fig. 5). Several of these nodules were umbilicated. The consistency of the liver was increased to grade 3. The cut surface of the liver was studded with malignant whitish yellow nodules, which had destroyed about two thirds of the hepatic parenchymatous tissue. The left lobe of the liver was decreased in size. There was no gross invasion of the larger portal or hepatic veins.

Microscopic sections (fig. 1 b) showed extensive invasion of the hepatic parenchyma by the malignant process. The cuboid to cylindric cells, with dark pyknotic nuclei and clear cytoplasm, were arranged in tubular form. In some areas the growth was less differentiated and more anaplastic; in these areas more mitotic figures were seen. The lumens of the alveoli were relatively small. They contained amorphous material and cellular debris. An abundant connective tissue stroma, containing relatively few lymphocytes, separated the alveolar elements. Many small blood vessels filled with blood were seen. The neoplasm appeared to be rather vascular and certainly of a high grade of malignancy. The hepatic parenchyma itself appeared to be normal, save for some amount of inspissated bile in the small biliary canaliculi. There was no evidence of cirrhosis. Histologically, this tumor was a cholangioma.
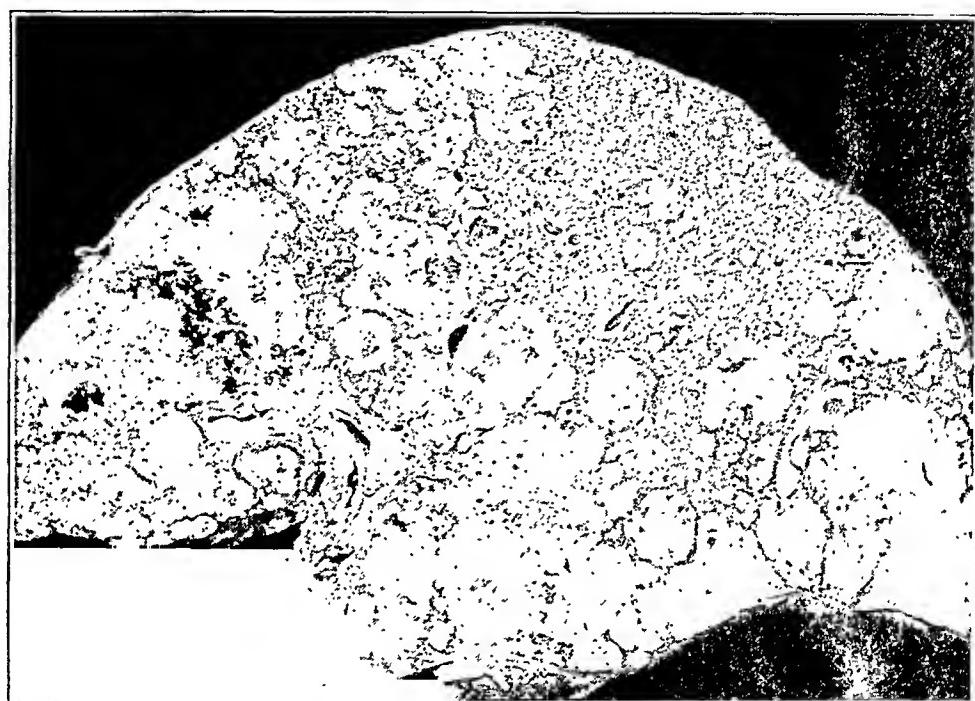
Fig. 5.—The liver in case 1. Note the multiple tumorous nodules throughout both lobes of the liver. Cirrhosis is not present.

CASE 2.—A man 57 years old was admitted to the clinic on May 25, 1933, complaining of a progressively growing ulcer on the lower lip. Results of physical examination otherwise were essentially normal. Blood cell counts were within normal limits, but urinalysis disclosed glycosuria. The value for fasting blood sugar content was 94 mg. per hundred cubic centimeters of blood, but the glucose tolerance curve was indicative of mild diabetes mellitus. The ulcerated labial lesion was excised; the pathologic report was "squamous cell epithelioma, grade 3." Later, dissection of the submental, submaxillary and upper jugular lymph nodes was performed; pathologic examination of these nodes did not show metastatic carcinoma. Convalescence of the patient was uneventful.

This patient returned on March 15, 1943. He was admitted directly to the hospital in a critical condition. For three months he had noted weakness, loss of weight and anorexia. His local physician had suspected gastric ulcer, but treatment with diet and alkaline powders had failed to help. He had become semistuporous and edematous within the preceding forty-eight hours.

Physical examination showed a dehydrated semistuporous man, whose breath had the odor characteristic of uremia. The systolic blood pressure measured 140 and the diastolic 70 mm. of mercury. The heart and lungs were normal. No abdominal masses were palpable. The prostate gland was slightly enlarged. Noticeable pitting edema of both lower extremities and abdomen was observed.

Urinalysis disclosed albuminuria of grade 2, no glycosuria and hyaline casts, grade 3. The hemoglobin content measured 11.2 Gm. per hundred cubic centimeters of blood, and the erythrocytes numbered 3,120,000 per cubic millimeter of blood. The leukocyte count was 15,300 per cubic millimeter of blood, and the differential blood count was as follows: segmented neutrophils 45, "band forms" 41, lymphocytes 9 and monocytes 5. Results of the flocculation test for syphilis were negative. A roentgenogram of the thorax demonstrated no abnormality. Data concerning
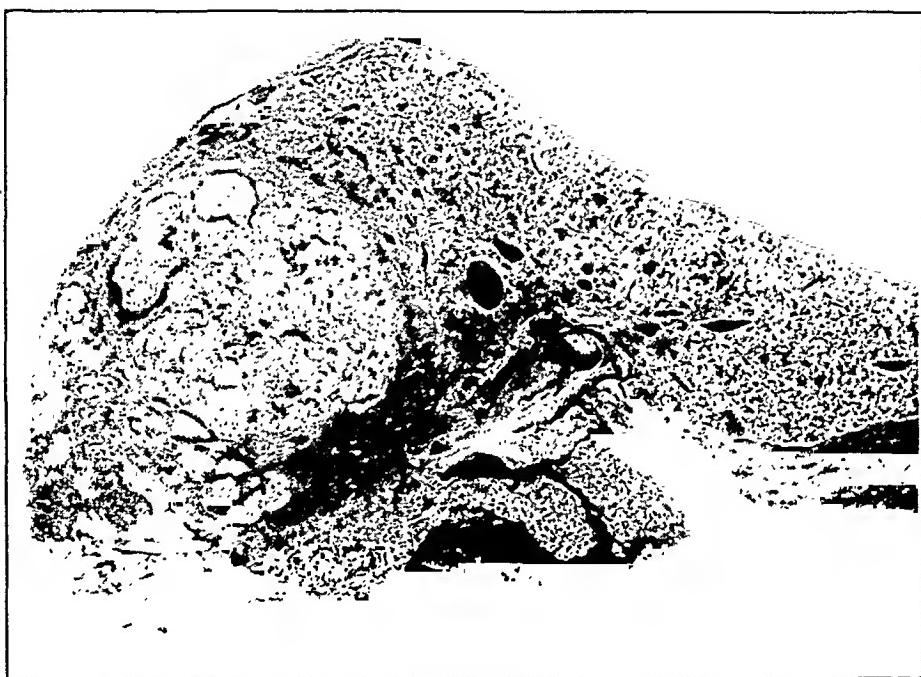
Fig. 6.—The liver in case 2. Note the large tumorous mass in the right lobe of the liver, with smaller satellite nodules around the periphery. Cirrhosis is distinct.

blood chemistry were as follows: urea content 266, creatinine content 2.6 and sugar content 147 mg. per hundred cubic centimeters of blood; chloride content 518, cholesterol level 66 mg., per hundred cubic centimeters of plasma, and calcium content 8.4 mg. per hundred cubic centimeters of serum. The carbon dioxide–combining power was 43.8 volumes per cent. The serum protein content measured 5.56 Gm. per hundred cubic centimeters of serum, and the albumin-globulin ratio was 1.18: 1.

The course of this patient was rapidly downhill. He lapsed into a profound coma, had a terminal bout of hematemesis and died four days after his arrival at the hospital. The prevailing clinical diagnosis was uremia, possibly on the basis of chronic nephritis.

Necropsy was performed twelve hours after the death of the patient. The report was cirrhosis of the liver, with malignant hepatoma invading the hepatic

vein and inferior vena cava; tumorous thrombosis of the lower vena cava and left renal vein; ascites; ruptured esophageal varices, with residual hemorrhage in the stomach; healing duodenal ulcer, with partial pyloric obstruction; edema and emphysema of the left lung, with beginning pneumonia; grade 2 .hypertrophy of the prostate gland; small calculus in the urinary bladder, with cystitis cystica of grade 2; two polyps and two lipomas of the cecum, and arteriosclerosis of grade 2.

There was edema of grade 3 of both lower extremities and of the entire back. The peritoneal cavity contained 2,000 cc. of cloudy amber fluid, but there were no signs of peritonitis. The spleen weighed 144 Gm. It appeared to be normal. The gallbladder contained 40 cc. of bile, and the mucosa appeared normal. The extrahepatic bile ducts and pancreas seemed to be normal. The esophagus contained several dilated, and ruptured varices and a few superficial longitudinal ulcers. The stomach contained 350 cc. of clotted blood and mucus. The duodenum was somewhat narrowed by a healing ulcer situated 1.5 cm. below the pylorus. The liver weighed 2,008 Gm. The surface was irregularly nodular and granular. The consistency was increased to grade 2. The cut surface was gray-yellow, and the markings were indistinct. Within the substance of the right lobe there was a soft yellowish pink mass measuring 5 by 7 cm. and surrounded by several smaller similar masses up to 1.5 cm. in diameter (fig. 6). The hepatic vein and the inferior vena cava were completely filled with an adherent thrombus which extended 1 cm. into the left renal vein and narrowed it about 50 per cent. No thrombus was found in the right auricle.

Histologic sections (fig. 2 b) showed an extensive amount of tumorous tissue, which was necrotic and hemorrhagic in some areas. The large polyhedral polygonal cells with vacuolated acidophilic cytoplasm and large, vesicular, frequently multiple nuclei and nucleoli were arranged in trabecular fashion and in cords. There were numerous multinucleated tumorous giant cells and many typical and bizarre mitotic figures. No evidence of intracellular bile pigment was discovered. Blood vessels were prominent, and the tumor appeared to be exceedingly vascular. The stroma was of the capillary type and contained numerous lymphocytes, especially near the hepatic parenchyma. Certain sections showed prominent invasion of the larger blood vessels by the tumorous cells. The hepatic parenchymatous tissue had been replaced by considerable dense fibrous tissue containing many bile ducts and lymphocytes. Numerous large and small regenerative nodules were seen to possess no biliary canaliculi or central veins. Histologically, this tumor was a highly malignant hepatoma, occurring in a decidedly cirrhotic liver.

SUMMARY AND CONCLUSIONS

Primary carcinoma of the liver is a rare disease. Thirty-one instances have been found in 16,303 necropsies at the Mayo Clinic, an incidence of 0.19 per cent. Six of the cases had been previously reported in the literature. The disease occurs most commonly in the Orient and South Africa. A series of reports collected from the literature reveals an incidence of 0.227 per cent among the white-skinned races of Europe and America and an incidence of 0.983 per cent among the Asiatic and African races. This increased tendency of the disease to afflict the latter peoples is believed to be due to the high geographic incidence of schistosomiasis and clonorchiasis among them and to the chronic irritation of the liver caused by these parasitic infections. Primary

carcinoma of the liver is a disease of older persons. In most of our cases the lesion occurred in the fifth, sixth and seventh decades of life. In 23 of our 31 cases the disease occurred in males, the sex which usually is more frequently afflicted. The primary carcinomas of the liver arising from hepatic cells are called "hepatomas," and those arising from bile ductules are called "cholangiomas." Reports of hepatomas in the literature far exceed those of cholangiomas. In 20 of our 31 cases the tumors were hepatomas, and in 11 they were cholangiomas. Cirrhosis frequently is associated with primary carcinoma of the liver and undoubtedly is an important causative factor. In 16 of our 20 cases of hepatomas (75 per cent) cirrhosis was associated, but it was present in only 2 of our 11 cases of cholangiomas (18.2 per cent). It is still debatable whether the incidence of primary carcinoma of the liver is any greater in the presence of hemochromatosis than it is when non-pigmentary cirrhosis alone is present. There are no pathognomonic clinical or laboratory signs or symptoms in these cases, and the diagnosis is rarely made before the death of the patient. The most significant symptoms and signs in our cases were emaciation, abdominal distention with ascites, abdominal pain, edema of the ankles, jaundice and a palpable abdominal tumor.

Gross distinction between hepatoma and cholangioma usually is difficult, and the final diagnosis must be made histologically. The question of multicentric or unicentric origin of these tumors is still debatable; most authors favor the latter view. Eleven of our 20 cases of hepatomas were characterized by obvious invasion of blood vessels. The early vascular involvement is thought to cause the intrahepatic metastasis so often seen in the presence of hepatoma. Tumorous thrombosis of the inferior vena cava and right auricle may accompany these tumors. In 21 of our 31 cases (67.7 per cent) extrahepatic metastasis was present. Cholangioma as a rule metastasizes earlier and more frequently than does hepatoma. The tumors under consideration grow exceedingly rapidly, and the prognosis usually is hopeless. Early surgical resection of the liver offers the only chance for cure.

HOMOLOGOUS SERUM HEPATITIS FOLLOWING TRANSFUSION

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JAUNDICE was an important medical problem in the European Theater of Operations after the American troops arrived in Northern Ireland and England in the early months of 1942. Until the late summer and fall of 1944 this jaundice was considered to be for the most part due to either infectious hepatitis or homologous serum hepatitis following the injection of yellow fever vaccine. In contrast, in many cases the jaundice seen following the invasion of Normandy, though belonging to the homologous serum group, differed in that the disease was transmitted by plasma, serum or whole blood instead of vaccine containing a human serum component.

With the ever increasing use of transfusions of blood and plasma, it seems pertinent to emphasize the occurrence and importance of homologous serum hepatitis following this therapeutic procedure. It is the purpose of this paper to review briefly some of the literature and to report a series of 14 cases of homologous serum hepatitis, with a detailed description of the 2 fatal ones and the important findings at autopsy.

The entity of homologus serum jaundice was first described by Lürman in 1885, in reporting the outbreak of jaundice among workers in a Bremen shipyard who had been vaccinated with a vaccine containing human lymph. From one to seven months after vaccination 191 out of 1,289 persons became jaundiced, while 500 other workers in the same shipyard, vaccinated with a different lot of lymph, remained free of the disease. No further report of jaundice following the use of human serum products appeared until 1937, when the phenomenon was reported by Findlay and MacCallum[1] as occurring in a number of persons several months after they had been inoculated with a yellow fever vaccine containing human serum. This was followed in 1938 by MacNalty's[2] report, in which he described similar cases in groups

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1. Findlay, G. M., and McCallum, F. O.: Note on Acute Hepatitis and Yellow Fever Immunization, Tr. Roy. Soc. Trop. Med. & Hyg. 31:297, 1937.

2. MacNalty, A. S.: Report of the Chief Medical Officer, Ministry of Health, London, His Majesty's Stationery Office, 1938.

of children given injections of pooled measles convalescent serum.   In recent years there have been numerous articles recording cases of jaundice following injection of yellow fever vaccine in England,[3] the United States,[4] Brazil [5] and the Virgin Islands [6]; mumps and measles convalescent plasma and serum in England,[7] and pappataci fever vaccine in Russia.[8]   The period of incubation in these cases ranged between thirty-five and one hundred and forty days, in the great majority being sixty to ninety days.

Morgan and Williamson [8] subsequently reported 9 cases of jaundice occurring seven to sixteen weeks after transfusions of plasma or serum, and Beeson [8a] has recorded the occurrence in 7 patients one to four months following transfusions of blood or plasma.[9]   Bradley and

3. (*a*) Findlay, G. M., and Martin, N. H.: Jaundice Following Yellow Fever Immunization, Lancet **1**:678, 1943.   (*b*) Homologous Serum Jaundice, Memorandum Prepared by Medical Officers of Ministry of Health, ibid. **1**:83, 1943. (*c*) Findlay and MacCallum.[1]

4. (*a*) Outbreak of Jaundice in Army, Circular Letter No. 95, Office of the Surgeon General, J. A. M. A. **120**:51 (Sept. 5) 1942.   (*b*) Jaundice Following Yellow Fever Vaccination, editorial, ibid. **119**:1110 (Aug. 1) 1942.   (*c*) Turner, R. H.; Snavely, J. R.; Grossman, E. B.; Buchanan, R. N., and Foster, S. O.: Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation with Yellow Fever Vaccine: Especial Consideration of Severe Attacks, Ann. Int. Med. **20**:193, 1944.

5. Fox, J. P.; Manso, C.; Penna, H. A., and Para, M.: Observations on Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever, Am. J. Hyg. **36**:68, 1942.

6. Findlay and Martin.[3a]   Fox and others.[5]

7. (*a*) Beeson, P. B.; Chesney, G., and McFarlan, A. M.: Hepatitis Following Injections of Mumps Convalescent Serum: I. Use of Plasma in the Mumps Epidemic, Lancet **1**:814, 1944.   (*b*) Hawley, W. L., and others: Hepatitis Following Injection of Mumps Convalescent Plasma: III. Clinical and Laboratory Study, ibid. **1**:818, 1944.   (*c*) McFarlan, A. M., and Chesney, G.: Hepatitis Following Injection of Mumps Convalescent Plasma: II. Epidemiology of the Hepatitis, ibid. **1**:816, 1944.   (*d*) MacNalty.[2]   (*e*) Footnote 3 *b*.

8. Morgan, N. V., and Williamson, D. A. J.: Jaundice Following the Administration of Human Blood Products, Brit. M. J. **1**:750, 1943.

8a. Beeson, P. B.: Jaundice Occurring One to Four Months After Transfusion of Blood or Plasma, J. A. M. A. **121**:1332 (April 24) 1943.

9. Since this paper was prepared and submitted to the Surgeon General's Office for approval for publication there have appeared two articles of a similar nature to this paper. E. M. Rappaport (Hepatitis Following Blood or Plasma Transfusions: Observations in Thirty-Three Cases, J. A. M. A. **128**:932 [July 28] 1945) reported 32 patients evacuated from theaters of combat in whom hepatitis developed nine to eighteen weeks following transfusions of blood or plasma. There were no fatalities. A. M. Snell, D. A. Wood and L. J. Meienberg (Infectious Hepatitis with Especial Reference to Its Occurrence in Wounded Men, Gastroenterology **5**:241, 1945) presented the findings of 32 patients in whom hepatitis developed in twenty-one to one hundred and forty days, with an average

others [10] have recently demonstrated, by the use of reconstituted human serum containing an icterogenic agent, that the length of the period of incubation and the severity of the disease are not appreciably influenced by the amount of serum administered or the parenteral route used. They gave injections in one group of patients using 0.1 cc. of serum intradermally, in a second using 400 cc. intravenously and in a third using both. In 57 per cent of the persons to whom injections were given hepatitis developed, and there were no significant variations in the severity of the disease or the length of the period of incubation.

The aforementioned clinical reports have been paralleled by experimental transmission of the disease to human volunteers, known icterogenic lots of vaccine having been employed and serum, blood or plasma from patients in the early stages of this disease.[11] Findlay and Martin [3a] claimed transmission of the disease by the use of nasal washings obtained from 3 patients in the preicteric stage of jaundice caused by post-yellow-fever vaccine. In their studies, the instillation of the filtered washings into the noses of 4 volunteers resulted in 3 cases of hepatitis.

MATERIAL

From Sept. 18, 1944 to Nov. 14, 1944 there were observed at the Seventh General Hospital 14 cases of hepatitis believed to be the result of transfusions of plasma administered forty-five to eighty-eight days before the onset of symptoms. Twelve of the patients were studied throughout the course; 1 arrived from a nearby station hospital three days after the onset of his jaundice and while still having acute symptoms, and 1 arrived from a general hospital in France three weeks after the onset of his jaundice and during his convalescent stage.

Twelve of these patients were battle casualties from France being treated for or convalescing from wounds received in combat. The remaining 2 received injuries in England, 1 a ruptured liver and the other a perforated hollow abdominal viscus. All had been continuously hospitalized since their injuries.

SUMMARY OF SERIES

Period of Incubation.—The period of incubation of the disease in this series, as determined from the date on which plasma or blood was first administered to the onset of symptoms, ranged from forty-three to eighty-eight days, with an average of sixty-three days (table 1). All

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of eighty-four days, following transfusions of blood and plasma. In 8 patients in this series there developed symptoms and signs of severe disease of the liver and involvement of the central nervous system, 6 of whom died. The mortality rate of 19 per cent is comparable to that of 15 per cent in our smaller series.

10. Bradley, W. H.; Loutit, J. F., and Maunsell, K.: An Episode of Homologous Serum Jaundice, Brit. M. J. **2**: 268, 1944.

11. (a) MacCallum, F. O., and Bauer, J. J.: Homologous Serum Jaundice: Transmission Experiments with Human Volunteers, Lancet **1**:622, 1944. (b) Oliphant, J. W.; Gilliam, A. G., and Larson, C. L.: Jaundice Following Administration of Human Serum, Pub. Health Rep. **58**:1233, 1943. (c) Oliphant, J. R.: Jaundice Following Administration of Human Serum, Bull. New York Acad. Med. **20**:429, 1944.

patients had received plasma or serum, and in addition 9 had had blood transfusions.

Clinical Picture.—The initial symptoms were usually malaise, lassitude, ease of fatigue, anorexia, low grade fever (only 4 patients having a temperature of 100 F. [orally] or over), chilliness, headache and generalized aches and pains in the joints. These symptoms were soon followed by nausea, often accompanied with vomiting, abdominal discomfort or pain, which was frequently localized by the patient in the epigastrium or periumbilical region, and change of bowel habits, constipation being more frequent than diarrhea. The patient usually noticed his urine becoming dark and the stools lighter, often clay colored. The presence of polymorphic cutaneous rashes, which is described in the literature [12] as being not unusual in homologous serum jaundice,

TABLE 1.—*Periods of Incubation and Duration of Symptoms in Fourteen Patients with Jaundice*

Case	Period of Incubation, Days	Duration of Preicteric Symptoms, Days	Icteric Period, Days	Length of Stay in the Hospital Due to Hepatitis, Days
1	45	3	5	Died
2	73	3	6	Died
3	79	4	14	25
4	80	3	41	83
5	66	3	30	63
6	52	8	35	70
7	80	3	25	49
8	88	9	17	45
9	74	9	5	26
10	54	13	16	47
11	62	5	8	24
12	43	No clinical icterus	No clinical icterus	7
13	57	2	35	37
14	69	3	21	35
Average	66	5.23	19.8	42.6

occurred in only one instance in this series. Icterus appeared two to thirteen days after the onset of symptoms (table 1). Table 2 gives the symptoms and signs of the patients comprising the present series.

The length of the symptomatic stage of infectious hepatitis and homologous serum jaundice varies greatly in the literature, and it is difficult to obtain definite information. The present symptoms lasted from eight to twenty-three days, and the period of jaundice ranged between five and forty-one days (table 1).

Course.—The usual course of this disease was that of a slow convalescence following the termination of the symptomatic stage, except in 2 cases in which it was fulminating, resulting in death. If this small group of cases is a true sample of the condition as a whole, the mortality rate as evidenced by 2 fatalities (15 per cent) is much higher

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12. Hawley, McFarlan and Steigman.[7b]   Footnote 3 *b*.   Turner, Snavely and Grossman.[4c]

than that in infectious hepatitis and even in the homologous serum jaundice following injection of yellow fever vaccine. The average stay of the patients in the hospital as a result of hepatitis was forty and one-half days, and on discharge from this hospital there was no evidence of residual damage to the liver. It is the impression that these patients were usually sicker and their course more protracted than that of patients with infectious hepatitis. The increased severity of symptoms, the protracted course and the higher mortality rate in this group of patients may be explained by the following facts: 1. Each had had moderate to severe wounds. 2. All but 2 had been in combat, where the diet is notoriously poor and monotonous. 3. Their general physical condition was not so good as that of the average patient seen with infectious hepatitis or hepatitis following injection of yellow fever vaccine.

TABLE 2.—*Symptoms and Signs in Fourteen Patients with Hepatitis*

Symptoms	No. of Cases	Percentage
Malaise	14	100
Nausea and vomiting	14	100
Anorexia	14	100
Dark urine	14	100
Abdominal discomfort	13	93
Jaundice	11	78
Light to clay-colored stools	10	71
Fever	9	64
Palpable liver	8	57
Constipation	8	57
Generalized aches and pains	5	35
Chills	4	21
Pruritus	1	7
Rash	1	7
Diarrhea	1	7
Palpable spleen	0	0

Complications.—In 1 patient ascites developed seven days after the onset of symptoms, at which time the total plasma protein content was 4.5 mg. per hundred cubic centimeters of blood, with an albumin-globulin ratio of 0.83. It is questionable whether the increase of peritoneal fluid can be attributed to the low plasma protein content, as this complication is known to occur without lowering of the albumin or globulin content of the plasma and has been ascribed by Lucke [13] to endophlebitis of the veins in the portal radicles of the liver.

In 2 of the patients in this series infections of the blood stream developed. In 1 patient suffering from hemiplegia of the right side as the result of a gunshot wound of the brain there developed acute pyelonephritis and bacteremia due to Aerobacter aerogenes. These infections were treated with sulfadiazine, and the patient recovered. In the second case, in which the disease was fatal, bacteremia caused by hemolytic Staphylococcus aureus developed, which was treated by

13. Lucke, B.: The Pathology of Fatal Epidemic Hepatitis, Am. J. Path. **20**: 471, 1944.

means of intermittent intramuscular and continuous intravenous infusions of penicillin, following which the blood stream became sterile.

REPORT OF CASES

The 2 cases in the present series in which the disease was fatal are of sufficient interest to warrant their being reported in detail.

CASE 1.—A 28 year old white soldier (C. M.) was wounded in action in France on Aug. 1, 1944 by a high explosive shell, sustaining a compound fracture of the radius of the left arm, multiple severe penetrating wounds of the right foot, with a traumatic amputation of the fifth toe, and a mild perforating wound of the middle finger of the right hand. He was evacuated to the aid station of his battalion shortly after being wounded, and there 1 unit (250 cc.) of reconstituted lyophilized plasma was administered and preliminary treatment of the wounds was performed. From there he was rapidly evacuated back into the Zone of Communications, reaching a station hospital in England on August 4. During the evacuation, on the day following that on which the patient was wounded, a second unit of plasma was given. Definitive treatment was given at the station hospital, following which the patient was transferred to this installation on August 14 in preparation for his movement to the United States.

The patient recovered rapidly and was soon up and about on crutches but did not leave the ward. However, on September 14 the onset of fever was noted, with a rise in temperature as high as 101.8 F. accompanied with malaise, lethargy, generalized aches and pains, moderate anorexia, nausea, vomiting when he tried to eat and mild pain in the right upper abdominal quadrant. Physical examination was noncontributory at this time, and the leukocyte count was 4,850, with a normal differential count. Administration of penicillin, 20,000 units every three hours, was started because of fear of an infection under the cast despite the absence of any symptoms referable to this site. The symptoms continued unchanged until September 17, when the temperature fell to normal and the patient noticed his urine to be dark red-brown, which by laboratory examination proved to be due to the presence of bile. He was then seen to be icteric. The character of the patient's stool was not observed. Physical examination at this time revealed a patient not acutely ill and only moderately uncomfortable due to generalized malaise, lethargy and continued nausea and vomiting. The liver was palpable 2.5 cm. below the right costal margin and was moderately tender; the lower edge was rounded and firm. The spleen could not be felt. The laboratory observations at this time revealed an icterus index of 62; a total plasma protein content of 5.7 mg. per hundred cubic centimeters, with an albumin-globulin ratio of 1.3, and a blood nonprotein nitrogen content of 44.4 mg. per hundred cubic centimeters. The prothrombin time was thirteen seconds (normal control, thirteen seconds), and bile and urobilinogen were present in the urine.

The patient was put on a high protein, high carbohydrate, low fat diet, of which actually he ate extremely little. During this entire period activity was not restricted.

Icterus continued to increase, nausea and occasional vomiting were still present and pain in the right upper abdominal quadrant continued. During the evening and night of September 19 the patient became increasingly drowsy and difficult to arouse. By the morning of September 20 it was impossible to arouse him, but he became increasingly restless and difficult to handle, so that by late morning he was absolutely uncontrollable whenever he was approached to be examined, administered medicaments or fluids or for any other purpose. It became necessary

to quiet him by means of intramuscular injection of paraldehyde so that fluids could be given. Three thousand cubic centimeters of 10 per cent dextrose in sterile water plus an additional 150 Gm. of dextrose was given intravenously during the next sixteen hour period. In addition, 10 cc. of whole crude liver extract, 50 mg. of thiamine hydrochloride, 40 mg. of vitamin K, 100 mg. of ascorbic acid and 10 mg. of riboflavin were given intravenously. On September 20 the icterus index was 82, the blood nonprotein nitrogen content was 52.6 mg. per hundred cubic centimeters and the plasma protein content was essentially unchanged. Examination of the urine continued to show the presence of bile and urobilinogen in a dilution of 1 : 320.

Despite this therapy the patient continued to get worse, so that by the morning of September 21 he was deeply comatose and quiet, and Cheyne-Stokes type of respiration had commenced. He was more deeply icteric, and examination revealed his liver to be just palpable below the right costal margin in the midclavicular line. The spleen still could not be palpated. At this time the peripheral blood contained 18,650 leukocytes, 73 per cent of which were polymorphonuclear leukocytes, and a 95 per cent hemoglobin content (Sahli). The icterus index had risen to 122.8, the prothrombin time was 100 per cent of normal, the blood cholesterol content was 153.6 mg. per hundred cubic centimeters, the blood nonprotein nitrogen content was 45.6 mg., the blood urea nitrogen content was 6.9 mg. and the blood plasma protein content was still unchanged. The same therapeutic regimen as that given on the previous day was repeated. In the afternoon of September 21 the temperature, pulse rate and respiratory rate began to rise. About midnight the patient began retching and then bringing up large quantities of coffee ground vomitus which gave a positive reaction (4 plus) to the guaiac test. This continued until his death at 2 : 30 on the morning of September 22.

The pertinent observations at autopsy are as follows:

1. The left pleural cavity contained approximately 1,500 cc. of dark brown fluid with the sour odor of gastric contents and was similar in appearance to that found in the stomach. The posterior and lateral parietal pleura was opaque, gray and shaggy as a result of digestion of the fluid just described. Microscopic examination revealed this digestion to be antemortem in type.

The esophagus at its point of exit through the diaphragm was bulging into the left pleural cavity, and a defect in the muscularis measuring 1 cm. in diameter was seen. This defect did not appear to continue into the lumen of the esophagus, and on careful search no ulceration or slit of the esophageal mucosa could be demonstrated. Esophageal varicosities could not be demonstrated.

2. Minimal bronchopneumonia at the base of both lungs was seen grossly and microscopically. No definite pathogenic bacteria were found bacteriologically.

3. The liver weighed 900 Gm. The edges were more pointed than usual, and the capsule was dull and wrinkled. The organ felt extremely firm and fibrotic and cut with difficulty. The cut surface was void of the usual lobular markings and was mottled with yellow and green-gray areas.

Microscopically, only an extremely small portion of the hepatic cords remained in the granular debris which represented the remnants of the hepatic cells. There was little inflammatory reaction throughout the liver; only a few scattered polymorphonuclear leukocytes, an occasional focus of plasma cells and scattered macrophages laden with hemosiderin were seen. In some areas there was hemorrhage into the granular debris. The bile ducts were conspicuous, owing to the loss of hepatic parenchyma, and many of these contained bile casts in their lumens. Sudan III stain revealed a moderate amount of intracellular lipid within the macrophages, Kupffer cells and remaining hepatic cord cells. No inclusion bodies could be found.

4. The spleen weighed 175 Gm. It was soft but otherwise revealed nothing unusual grossly or microscopically.

5. The stomach contained about 500 cc. of red-brown sour-smelling contents. The mucosa was edematous and moderately red, due to engorged blood vessels. The edema and redness due to congestion was present throughout the small intestine. Pale gray stools were present in the rectum.

6. The kidneys were grossly normal and microscopically showed no evidence of a biliary nephrosis.

7. The brain showed nothing unusual grossly or in many microscopic sections taken from the cerebral cortex, cerebellum and medulla.

CASE 2.—A 30 year old white soldier was wounded in action in France on July 11, 1944, receiving a severe penetrating wound of the left buttock and a severe compound comminuted fracture of the entire upper one third of the left femur and associated destruction of the left sciatic nerve. On the first day of his injury he was given 2 units of reconstituted lyophilized human plasma and preliminary treatment of his wounds, definitive treatment taking place in a station hospital on July 12. He was gradually evacuated to England and finally reached the Seventh General Hospital on July 31, where further operative treatment of his severe fracture was done on September 1, at which time he received 500 cc. of human whole blood and 1 unit of plasma.

The patient did well, rapidly recovering his strength and feeling of well-being. He was, of course, confined to bed because of the spica cast which he wore.

On September 23 he began to have a low grade fever and slight malaise but no other symptoms. His temperature rose the following day, and slight anorexia was present but otherwise he felt well. The blood cell count on September 25 showed no leukocytosis, and no real symptoms of infection seemed to be present. The clinical picture continued unchanged until September 26, at which time the patient noted "funny feelings" in his epigastrium, increased malaise, moderate anorexia, nausea, chilliness and the fact that his urine was dark. He did not observe the character of his stools. Later in the day he was found to be slightly icteric, and the liver was found to be tender and palpable just below the right costal margin. The spleen could not be felt. He was given a high protein, high carbohydrate and low fat diet, which he could only partially eat. However, he did not vomit. Two multivitamin capsules were given with each meal. The following day, icterus was more striking and the appetite less and he vomited once after the noonday meal. By September 28 icterus was pronounced, but the temperature was normal most of the day and the patient seemed to feel much better. However, on the evening of September 29, the seventh day after the onset of this complication, he became drowsy, and by the following morning he was extremely difficult to arouse. Despite this fact he was becoming exceedingly restless, moving about in bed continually. In addition, he began to get incoherent in his speech, and by afternoon he was entirely disoriented. Physical examination at this time revealed him to be moderately icteric. Neither the liver nor the spleen was palpable. The laboratory data on the morning of September 30 were as follows: hemoglobin content, 97 per cent (Sahli); red blood cells, 4,720,000; white blood cells, 11,000, of which 85 per cent were polymorphonuclear leukocytes; icterus index, 57.9; serum bilirubin content, 9.0 mg. per hundred cubic centimeters, with a direct reaction to the van den Bergh test; total plasma protein content, 9.07 mg., with an albumin-globulin ratio of 1.36; prothrombin time, thirteen seconds (normal control, thirteen and one-half seconds); blood sugar level, 206 mg.; blood nonprotein nitrogen content, 48.5 mg., and blood urea nitrogen content, 13.8 mg. per hundred cubic centimeters. The urine was normal

except for bile and urobilinogen present in a 1 : 640 dilution. It was not until the afternoon of September 30 that a culture of the blood taken on September 25 was found to have pathogenic growth, and this was recognized tinctorially and morphologically to be hemolytic Staph. aureus. The patient was then given 200,000 units of penicillin in a continuous intravenous infusion of 3,000 cc. of 10 per cent dextrose in water during the next fourteen hours. In addition, he was given 30,000 units of penicillin intramuscularly every two hours when the intravenous medication was not being administered. Additional therapy consisted of 10 Gm. of methionine in 500 cc. of isotonic solution of sodium chloride given intravenously and intravenous administration of 10 cc. of whole liver extract, 40 mg. of vitamin K, 50 mg. of thiamine hydrochloride, 20 mg. of riboflavin and 100 mg. of ascorbic acid.

The patient continued to get worse, being in deep coma by the morning of October 1. At this time the peripheral blood had 5,540,000 red blood cells, a hemoglobin content of 103 per cent (Sahli) and 20,750 leukocytes, of which 89 per cent were polymorphonuclear leukocytes. The icterus index had risen to 105, with a serum bilirubin content of 24.8 mg. per hundred cubic centimeters; the total plasma protein content was 6.8 mg. per hundred cubic centimeters, with an albumin-globulin ratio of 1.2; the prothrombin time was fourteen seconds (normal control, fourteen seconds); the blood nonprotein nitrogen content was 37 mg. per hundred cubic centimeters, and the blood urea nitrogen content was 11.8 mg. The urine still contained bile and urobilinogen; no tyrosine or leucine crystals were present. Administration of all the aforementioned medicaments, including penicillin in the same dosages and routes, was repeated. Cheyne-Stokes type of respiration appeared by noontime, and by early afternoon he began vomiting varying amounts of coffee ground-colored material, which gave a strongly positive reaction to the guaiac test. The patient continued in this condition, never regaining consciousness, and he died at 7 : 05 the morning of October 2.

The essential observations at necropsy were as follows:

1. Minimal bronchopneumonia was seen microscopically at the bases of both lungs.

2. The liver weighed 800 Gm. The capsule was thin, transparent and wrinkled. The organ had ropelike consistency and cut with decidedly increased resistance. The cut surface was mottled gray-yellow, with small diffusely scattered strands or gray, suggesting fibrous stroma, and interspersed yellow-gray areas resembling abnormal hepatic cells. The gallbladder and bile ducts were normal in appearance and contained clear gray-white mucoid bile. Microscopically, examination of the liver showed only a few scattered distorted hepatic cords remaining. The vast majority were represented by granular debris. The portal areas were infiltrated by a moderate number of polymorphonuclear leukocytes, plasma cells and lymphocytes. The capillaries were greatly engorged with blood, and in areas there appeared to be hemorrhage into the hepatic stroma. Scattered macrophages contained hemosiderin. No bile casts were present in the bile ducts. No endophlebitis could be seen. Sudan III stain revealed a moderate amount of fat within the remaining parenchymal cells and the macrophages. Inclusion bodies could not be seen.

3. The spleen weighed 230 Gm. and was soft. The capsule was taut and purple-gray. On section, the pulp was soft and purple-gray, and the usual markings were not prominent. Microscopically, the findings were those of acute splenitis.

4. The gastrointestinal tract showed an engorged edematous mucosa throughout the stomach and small intestines. This portion of the tract contained material of

a coffee ground appearance, but no point of hemorrhage could be found. The rectum contained gray formed feces.

5. The kidneys were entirely normal, as were the bone marrow and the brain.

6. The wound of the buttocks and the compound fractured femur showed no evidence of infection, and, culturally, no pathogenic bacteria were found. The culture of blood taken from the heart showed no pathogenic growth.

Comment.—These 2 cases demonstrate the importance of the onset of drowsiness and/or restlessness at any time during this disease as important prognostic signs in prediction of the future course. Irritability, disorientation, irrationality, loss of memory and vague changes in the personality are likewise indications of the onset of a more serious stage of the illness or of a relapse.

A ruptured esophagus resulting from constant vomiting and retching was described by Weiss and Mallory [14] occurring in a patient who drank excessively. The finding of gastric contents in the pleural cavity of the patient in case 1 is probably an example of a ruptured esophagus by the same mechanism, despite the fact that the actual mucosal tear could not be demonstrated at autopsy.

LABORATORY OBSERVATIONS

The laboratory tests found most useful in the early diagnosis of this disease were the icterus index or test for serum bilirubin, the latter being the most delicate and accurate test, and the examination of the urine for bile and urobilinogen. These tests were also the most important ones in following the course of the illness. The level of the serum bilirubin was of great aid in determining when the patient should first be allowed out of bed and how much activity he should be permitted. Patients seemed to do best if activity was definitely restricted until the serum bilirubin level was down to 2 mg. per hundred cubic centimeters; if activity was allowed before this time, a rise in the level of the serum bilirubin of 1 to 2 mg. per hundred cubic centimeters could be demonstrated, and in 1 case mild clinical symptoms developed.

The determination of the total plasma protein content, the albumin and globulin levels and the prothrombin time was likewise valuable in following the course of these patients. There was a slight to moderate fall of the plasma protein content in all cases in which sufficient data could be collected, and in 1 case the level fell to 4.5 mg. per hundred cubic centimeters, and the patient clinically exhibited signs of ascites. In most patients there was a slight fall in the plasma prothrombin level, but in all it returned to normal limits without requiring the use of vitamin K. In the 2 fatal cases, vitamin K was administered paren-

14. Weiss, S., and Mallory, G. K.: Lesions of the Cardiac Orifice of the Stomach Produced by Vomiting, J. A. M. A. **98:** 1943 (April 16) 1932.

terally and no definite increase in the prothrombin time occurred. In no cases were the blood sugar levels unusual, except for the second fatal one, in which the initial blood sugar level was elevated to 206 mg. per hundred cubic centimeters. The blood picture was similar to that seen in infectious hepatitis, namely, a normal leukocyte level accompanied frequently with a lymphocytosis and the presence of atypical lymphocytes which are not unlike the cells in infectious mononucleosis but distinguishable from them. In the 2 fatal cases a leukocytosis developed terminally, with an increase in the polymorphonuclear elements. Table 3 gives the details of the laboratory observations.

The hippuric acid excretion test for hepatic function was not felt to be a reliable one for following the course of the disease, as its results are so dependent on normal urinary excretion. It was demonstrated by Neefe and others,[15] and confirmed in this series, that early in the course of the disease there is frequently oliguria, and during the convalescent period there may be great variations in the intake and output of fluid, which are not predictable. On many days, the output will exceed the intake, whereas at other times the output will be less than half the fluid consumed. However, as the convalescent period approaches its termination, the ratio of intake to output of fluid becomes that of a normal person, and the hippuric acid excretion test becomes of considerable aid in the estimation of residual hepatic damage. In only 1 patient was the excretion below normal standards at the time of his discharge from the hospital, which was necessitated by circumstances beyond control. An increased serum bilirubin level likewise indicated residual hepatic damage at that time.

Bacteremia developed in 2 patients in this series, which may be an indication of increased susceptibility to infections in the blood stream in this disease.

TREATMENT

The treatment of hepatitis due to homologous serum jaundice is the same as that of infectious hepatitis. High protein, high carbohydrate and low fat diet is the basis of therapy. The diet was supplemented with at least 1 quart (1,000 cc.) of powdered skim milk a day, this being made up in triple strength so that it afforded 72 Gm. of extra protein daily, with its accompanying high methionine content. The milk can be made more palatable by the use of malt, vanilla and other similiar ingredients. Sweetened fruit juice and hard candy in large quantities were given to these patients. Extra vitamins were given in all cases, with a special emphasis on the vitamin B complex. Casein digest administered orally as well as methionine administered intra-

15. Neefe, J. R.; Miller, T. G., and Chornock, F. W: Homologous Serum Jaundice: Review of the Literature and Report of a Case, Am. J. M. Sc. **207**: 626, 1944.

TABLE 3.—*Laboratory Data for Fourteen Patients with Hepatitis*

| Case | Urine | | | Hemoglobin % | White Blood Cell Count* | Differential Counts | Non-protein Nitrogen, Mg./100 Cc.* | Total Protein,† Mg./100 Cc. | Albumin-Globulin Content† | Pro-thrombin, per Cent of Normal† | Blood Chemistry | | Hippuric Acid Excretion at Discharge, Gm. | Hetero-phil Agglu-tinin |
	Bile	Urobil-inogen*	Albumin								Icterus Index*	Serum Bilirubin,* Mg./100 Cc.		
1	+	1:320	++	90	18,650	Polymorphonuclears, 73% Lymphocytes, 23%	52.6	5.7	1.0	100	122.8	....	...	...
2	+	1:640	++	97	20,250	Polymorphonuclears, 89% Lymphocytes, 11%	48.5	6.8	1.2	100	105	....	...	...
3	+	1:160	+	87	7,900	Polymorphonuclears, 44% Lymphocytes, 49% few atypical	30	5.0	1.1	60	46	10.3	3.9	...
4	+	1:40	++	84	9,350	Polymorphonuclears, 70% Lymphocytes, 24%	34	4.5	0.83	80	115	30.5	3.8	1:256
5	+	1:40	++	95	8,100	Polymorphonuclears, 39% Lymphocytes, 50% few atypical	31	5.7	1.1	80	54	9.3	5.0	Normal
6	+	1:20	+	92	9,450	Polymorphonuclears, 37% Lymphocytes, 40% few atypical	29	5.9	1.1	76	130	37.5	4.8	Normal
7	+	1:80	+	90	8,950	Polymorphonuclears, 53% Lymphocytes, 38%	33	5.7	1.8	100	51	9.4	4.0	Normal
8	+	1:20	0	80	12,300	Polymorphonuclears, 53% Lymphocytes, 41%	35	5.5	1.1	100	53	14.4	3.7	Normal
9	+	1:320	+	85	12,940	Polymorphonuclears, 50% Lymphocytes, 42%	30	5.9	1.2	100	....	1.8	3.7	Normal
10	+	1:80	0	85	10,200	Polymorphonuclears, 37% Lymphocytes, 54% few atypical	....	6.3	1.8	100	....	11.3	3.0	
11	+	1:80	0	92	7,500	Polymorphonuclears, 45% Lymphocytes, 46%	33	5.7	1.36	90	....	4.6	4.1	1:64
12	+	1:20	0	87	11,900	Polymorphonuclears, 72% Lymphocytes, 22%	....	...	...	...	....	1.3	5.1	Normal
13	+	1:40	++	76	11,600	Polymorphonuclears, 44% Lymphocytes, 44%	28	6.2	1.0	100	....	10.9	3.2	Normal
14	+	1:10	0	..	......	....	....	...	...	100	....	2.7	4.1	Normal

* Highest significant value. † Lowest significant value.

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venously was used in a few cases, but it was not possible to draw any conclusions as to their efficacy. During the acute stages of the disease when nausea and vomiting were present, liver, plasma and intravenous injection of dextrose were used to supplement the insufficient diet. Tincture of belladonna or atropine given before meals during the acute stage seemed to be helpful in relieving the aversion to food and the nausea caused by it.

<div align="center">COMMENT</div>

The main clinical points of differences between homologous serum hepatitis and infectious hepatitis are (1) period of incubation, (2) mode of spread and (3) severity. The period of incubation in the majority of cases of homologous serum hepatitis ranges between sixty and ninety days, whereas infectious hepatitis has a somewhat shorter period of incubation, averaging about thirty days. Homologous serum hepatitis is spread by the parenteral injection of human blood or its products by means of transfusions, convalescent serums, vaccines and contaminated syringes. The mode of spread of infectious hepatitis is still not completely known, but there is evidence that it may be transmitted by means of air-borne droplets and ingestion of material contaminated by the virus, namely, food and water. The severity of homologous serum hepatitis, as evidenced by the mortality rate in this series of cases and of the epidemic following injection of yellow fever vaccine,[16] is considerably greater than that seen in infectious hepatitis.

The pathologic changes of these two diseases are indistinguishable, as shown by Dible and others [17] by means of biopsies of material aspirated from the liver performed during various stages of the clinical courses. The clinical picture itself likewise has few distinguishing features to aid in differentiation of these entities.

The reasons for considering jaundice in these cases as being due to homologous serum, rather than being merely infectious hepatitis, are as follows: First, during the period in which these cases were being discovered in the surgical service, cases of infectious hepatitis in the medical service were infrequent. Similarly, cases of infectious hepatitis were not common in other hospitals during this period. Secondly, all these patients had been in a hospital at least six weeks, so that the only contact which they could have had with infectious hepatitis would have been with personnel of the hospital. Ten of the patients were in the hospital in which the onset of hepatitis occurred for over thirty days (table 4). Thirdly, it is known to be unusual for infectious hepatitis to develop in patients while hospitalized for another disease when the

16. Lucke.[13] Footnote 4 *a*.

17. Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Pathology of Acute Hepatitis: Aspiration Biopsy Studies of Epidemic, Arsenotherapy and Serum Jaundice, Lancet **2**:402, 1943.

stay in hospital is longer than the period of incubation of infectious hepatitis. Fourthly, all the patients in whom hepatitis developed during this period were in the surgical service and had had plasma and often blood administered from forty-three to eighty-eight days before.

In view of the huge amount of plasma, serum and whole blood being used during both war and peace, the resulting cases of hepatitis of the homologous serum type may be numerous enough to be of considerable importance, as were the cases resulting from the previously used yellow fever vaccine which contained a human serum component. Even if large numbers of these cases are not encountered, enough will occur so that it is essential for the disease to be recognized and treated as such at the earliest possible time.

Since this type of hepatitis may occur in extremely mild form and even without jaundice, it is important that all physicians be on the alert to recognize it, so that all factors which may cause an otherwise mild or subclinical form of the disease to become a severe one may be avoided.

TABLE 4.—*Length of Stay in Hospital in Which Onset of Hepatitis Occurred*

Stay in the Hospital, Days	No. of Patients
Less than 20	3
21 to 30	1
31 to 48	2
More than 48	8

The onset of symptoms in this disease does not always herald its future course, and in many with a mild insidious onset severe and prolonged symptoms develop. In the 2 fatal cases in this series the patients had mild symptoms during its inception, but soon they became seriously ill and the course was fulminating. Therefore, it is important not only that the disease in these cases be recognized early and in its mildest forms but that it receive vigorous treatment.

Many of the patients in whom hepatitis of this type developed were either ready to be evacuated to the Zone of the Interior or in need of secondary definitive surgical treatment. Neither evacuation nor surgical treatment should be allowed during this disease. These patients should not receive either oral or intravenous administration of barbiturates during the active stage of the disease, nor should they be subjected to anesthesia by inhalation of ether until complete recovery has taken place. Detoxification of most barbiturates takes place in the liver, and in the presence of diffuse damage of this organ barbiturate poisoning may occur when otherwise nontoxic doses of these drugs are used. Ether is a hepatotoxic agent, and its use is dangerous when the liver is acutely damaged. The danger of surgical intervention in patients with hepatitis lies not only in the deleterious effects of preoperative

medication and anesthesia but in the physiologic effects of surgical trauma as well. The role of the liver in the storage and synthesis of vitamins, blood clotting and general nutrition and their relation to the healing process makes any operation during the course of hepatitis inadvisable. Thus mild and often previously unrecognized hepatitis may be made considerably worse by operative procedures, and even a fatal outcome may result. Two of the patients in this series had operations postponed until the recovery from hepatitis was complete. As mentioned before, many of these patients were ready to be evacuated to the Zone of the Interior. Six of the 14 patients observed were ready to be sent to the United States at the time of the onset of their illness. Two had already been started on this evacuation when their disease was recognized; of these, 1 had been made worse by a short journey of 35 miles (56 Km.) as judged by clinical and laboratory observations; the other had had the onset of his symptoms three weeks preceding movement to this hospital from France, and the journey seemed to have no effect on the liver as far as symptoms were concerned. Laboratory data on this patient were inadequate prior to entry to this hospital. Therefore, since travel may aggravate the disease or precipitate a relapse, it is our opinion that patients should not be transported until recovery has taken place. In addition, nausea, vomiting and retching as a result of seasickness or airsickness occurring en route might be harmful.

The problem as to the infectivity of these patients is as yet unanswered. If the nasopharyngeal secretions are actually infectious, as the experiments on transmission of Findlay and Martin[3a] would indicate, the spread of this disease to personnel and other patients of the ward would be possible. The spread by means of syringes used in routine laboratory work may occur. It has not yet been clearly demonstrated whether the agent causing the disease can be transmitted by the feces. There has been no known secondary spread of the disease in our series.

SUMMARY

Fourteen cases of hepatitis of the homologous serum type, following the administration of plasma and blood forty-three to eighty-eight days before the onset of symptoms, are briefly described and discussed. The fact that this disease may become of great importance at this time when tremendous quantities of human blood and its products are being given therapeutically is brought to the general attention of physicians, and the importance of recognizing this entity and treating it vigorously is discussed.

Two fatal cases, with the observations at necropsy, are described in detail.

Sixty-Sixth Street and York Avenue, New York.

INTRATRACHEAL PENICILLIN THERAPY IN SUPPURATIVE BRONCHIECTASIS

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THE SURGICAL removal of one or more lobes of the lungs is now the accepted treatment for chronic suppurative bronchiectasis. About half the patients who suffer from this dreadful ailment are unable to undergo operation, however, because their lesions are too extensive or because they are poor surgical risks. I have sought to determine whether local penicillin therapy would help control the infectious element in the disease and thus reduce the amount of sputum in the non-surgical and surgical patients. It was not anticipated that the drug would in any way affect the anatomic deformity of the bronchial tree.

A 62 year old dentist with bronchiectasis of the lower lobe of the left lung presented himself at the Mount Sinai Hospital in June 1944 (case 1). His illness started two and one-half years earlier with suppurative bronchopneumonia, and, after a continual febrile course for eighteen months, he had been sent to Arizona. He remained there for one year, without change in his symptoms. He coughed with little interruption and expectorated fetid, purulent sputum, the amount of which measured 120 to 180 cc. daily. Then he had a hemoptysis of 500 cc. and was returned East for further therapy, possibly lobectomy. Here, the diagnosis of saccular bronchiectasis in a shrunken lower lobe of the left lung was confirmed by bronchoscopy and bronchography. His blood pressure was 216 systolic and 110 diastolic, and his electrocardiogram showed evidence of myocardial damage. He was considered a poor risk for lobectomy, and penicillin therapy was decided on.

In order to bring the highest possible concentration of the drug to the affected bronchi, local therapy was combined with intramuscular injections. Intrabronchial instillations were favored, rather than inhalation of a nebulized mist, because of the notable induration and shrinkage of the diseased lobe. It was felt that the mist would tend to enter the bronchi of the normally respiring pulmonary areas and that lesser amounts would gain access to the indurated lobe with its impaired ventilatory efficiency. On the other hand, bronchography had already shown that the sacculations could be filled by instillation.

The patient was given 15,000 units of penicillin sodium intramuscularly every three hours. By the third day the sputum decreased in quantity to 30 cc. in twenty-four hours. On this day, after preliminary postural drainage, 10,000 units of penicillin sodium dissolved in 100 cc. of isotonic solution of sodium chloride was instilled into the lower lobe of the left lung by means of a soft rubber catheter. The tube was introduced under fluoroscopic control after the larynx and trachea

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were cocainized. The patient was then placed in bed in a sitting position, leaning toward the left, and was cautioned against coughing during the next two hours. There were no signs of bronchial irritation following the treatment. The instillations were given daily, and the dose was increased to 25,000 units in the same amount of isotonic solution of sodium chloride. After the second intrabronchial instillation, on the seventh day of the intramuscular course, there was no more sputum

The patient lost his cough and slept undisturbed for the first time in two and one-half years. Administration of the drug was continued by both routes for five days, and then the intramuscular injections were stopped. The instillations were continued to a total of eleven. The patient was given, in all, intramuscular injections for four days, combined therapy for five and intrabronchial treatment alone for six days. He received a total of 1,060,000 units of penicillin, 260,000 units of which was given intrabronchially. He left the hospital, without symptoms, after a three weeks' stay and has remained under observation since.[1]

This surprisingly favorable immediate result prompted further trial of the method.

MATERIAL

During 1944 and 1945, 13 adults with chronic suppurative bronchiectasis and 1 child with suppurative pneumonia and early bronchiectasis were treated. Three of these patients were judged suitable for

TABLE 1.—*History and Extent of Involvement*

Case	Age, Yr.	Sex	Duration of Symptoms Yr.	Lobes Involved with Bronchiectasis
1 (M. J.)	63	Male	2½	Lower lobe of left lung
2 (M. S.)	30	Female	28	Right lung, lower and middle lobes; left lung, lower lobe
3 (J. N.)	63	Male	25	Lower lobes of both lungs
4 (T. M.)	26	Female	24	Both lobes of left lung
5 (G. B.)	37	Male	2½	Lower lobe of left lung
6 (A. E.)	33	Female	16	Lower and middle lobes of right lung
7 (J. T.)	50	Male	16	Lower and middle lobes of right lung
8 (H. H.)	63	Female	30	Right lung, all lobes; left lung, upper lobe
9 (M. S.)	52	Male	6	Lower lobes of both lungs
10 (J. I.)	20	Male	15	Right lung; lower and middle lobes; left lung, lower lobe
11 (B. R.)	17	Female	7	Right lung, all lobes; left lung, upper lobe
12 (J. G.)	25	Male	17	Right lung, lower and middle lobes; left lung, both lobes
13 (S. K.)	50	Male	18	Lower lobe of left lung

lobectomy. Two had lobectomy after preliminary penicillin therapy, with a definite cure. One is still considering the operation. In all instances the extent of the disease was determined by bronchography, and in 10 patients the disease was multilobar. The main lesions were in the bronchi of the lower lobes of both lungs and of the middle lobe of the right lung. Eleven patients had extensive sacculations in the affected lobes. Two had cylindric dilatations. Bronchography revealed shrinkage of the involved lobes in all patients. The symptoms had endured ten or more years in 9 patients (table 1). All patients were

1. Siltzbach, L. E.: Penicillin Therapy in a Case of Chronic Suppurative Bronchiectasis, J. Mt. Sinai Hosp. **12**:825 (July-Aug.) 1945.

expectorating at least 40 cc. of purulent sputum daily, and in 7 cases the sputum was decidedly fetid.

METHOD OF TREATMENT

After the first 2 patients were treated, the technic was changed from intrabronchial to intratracheal instillations. The drug was introduced into the trachea through a Mosher laryngeal life saver—a metal tube—and was directed to the desired lobe by positioning of the patient. The individual dose of penicillin was increased to 100,000 units, and the diluent of isotonic solution of sodium chloride was reduced to 20 cc. The lesser volume of fluid was better borne.

The patients received a course of seven to fifteen instillations over a period of eleven to eighteen days. Treatments were given daily or on alternate days. The instillation therapy was not instituted until the patient's course had become afebrile. Ten of the patients also received 15,000 to 30,000 units of penicillin intramuscularly every three hours, and in 3 instances the injections were continued along with the instillations. Four patients were treated with inhalations of nebulized penicillin in doses of 50,000 units per cubic centimeter four times daily, three before the instillations were begun and one after they were completed. Five had sulfonamide drugs orally before instillations were initiated. In general, instillations were begun when no further beneficial effect was obtained with the other methods of treatment.

SIDE EFFECTS

Half the patients had a moderate rise in temperature about six hours after some instillations. The fever generally lasted for a few hours and, with 1 exception (case 13), was not associated with roentgenologic evidence of extension of the infiltrations. In the exceptional case an extension was noted in the region of the old lesion after the seventh instillation and the treatment was discontinued. After six days the roentgenogram of the chest showed resorption of the infiltration, with a return to the previous status. It is of interest that shortly after this episode there developed in the patient an urticarial rash, which also disappeared within a few days. In another patient a transient rash and eosinophilia developed, and in still another there developed eosinophilia without any other allergic manifestation.

LEVELS OF PENICILLIN IN THE SPUTUM

In order to learn whether the instilled penicillin was being retained in the bronchial tree for significant periods, the concentrations of penicillin in the sputum were determined at intervals of one to five days after an instillation. Thirty-seven specimens were analyzed. Of eighteen specimens which were obtained twenty-four hours after instillation, sixteen revealed concentrations of 0.12 to 100 units per cubic centimeter of sputum. Twelve of these specimens had more than 1.0 unit per cubic centimeter. Eight out of twelve specimens obtained after forty-eight hours contained penicillin, the highest concentration being 10 units per cubic centimeter. Even after seventy-two hours four out of five

specimens contained the drug, one of them containing 5.5 units per cubic centimeter. Two specimens, obtained four and five days after an instillation, did not contain the drug. Penicillin administered intramuscularly could not be recovered from the sputum even when the doses by this route were as large as 400,000 units a day.

PENICILLIN IN EXCISED PULMONARY TISSUE

In 1 case there was an opportunity to ascertain whether the instilled drug was reaching the diseased portions of the lung. Forty-eight hours before lobectomy, 100,000 units of penicillin dissolved in 20 cc. of isotonic solution of sodium chloride was introduced intratracheally into the affected lobe. Intramuscular injections of penicillin were withheld for three hours preoperatively. A sample of blood drawn while the lobe was being removed contained no penicillin. On the other hand, several pieces of pulmonary tissue with diseased bronchi contained a concentration of 0.4 unit of penicillin per gram of pulmonary substance.

BLOOD LEVELS AFTER INSTILLATIONS

It was to be anticipated that following the intratracheal instillation of large doses of penicillin its presence would be detectable in the blood. In all specimens drawn within four hours, concentrations of at least 0.13 unit per cubic centimeter of serum were found. Peak levels occurred twenty to thirty minutes after the instillations. The highest was 4.0 units per cubic centimeter of serum thirty minutes after instillation of 100,000 units in 20 cc. of isotonic solution of sodium chloride. The concentrations of penicillin in the blood and sputum roughly paralleled the size of the dose instilled.

CHANGES IN CHARACTER OF SPUTUM WITH TREATMENT

The sputum changed in character after the first three or four instillations. In the 7 cases with fetid sputum the odor was abolished. In most instances the sputum became less purulent and more mucoid. Its bacterial flora also was altered. In general, the gram-positive organisms, such as Streptococcus viridans, Staphylococcus aureus and Staphylococcus albus, diminished or disappeared, and for the most part only gram-negative organisms—Escherichia coli and Hemophilus influenzae—could be cultured. In 1 case a bronchoscopic specimen obtained twenty-four hours after an instillation was sterile on aerobic and anaerobic culture. The usual respiratory flora tended to recur in about one week after the instillations were terminated. No relation appeared between the response to treatment and the sensitivity to penicillin of the predominating organisms or the disappearance of any single organism from the sputum.

Changes in the average volume of sputum in twenty-four hours were measured. These changes are a crude criterion, but one could not utilize alterations in the roentgenologic shadows of the lungs, since their pattern is usually set in patients with chronic suppurative bronchiectasis.

A pretreatment base line was established by measuring the volume of sputum in twenty-four hours for about one week while the patient practiced postural drainage. Three days were allowed for the drug to take effect. Then the daily volume of the sputum for the remaining period of therapy was averaged.
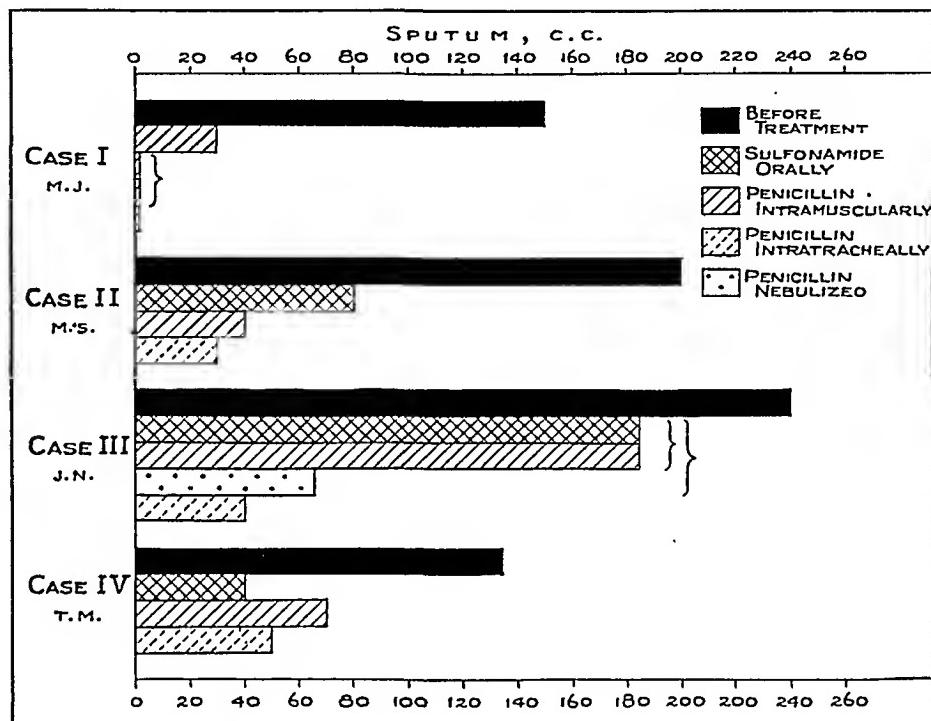
Fig. 1 (cases 1 to 4).—Average volume of sputum in twenty-four hours under specified therapy administered successively. Brackets indicate combined therapy. The lowest bar in case 1 represents the volume of sputum under intratracheal therapy alone.

A patient's response to therapy was considered poor if there was a reduction in the amount of sputum of less than 50 per cent, fair if the decrease was 50 to 80 per cent, good if the decrease was above 80 per cent and excellent if expectoration ceased. The immediate results of treatment are shown in figures 1, 2 and 3. The late results, after six to twenty-one months' follow-up observation, are given in table 2.

SUMMARIES OF CASES

CASE 1.—The course of the disease in the 62 year old dentist has been described. Before treatment he expectorated 150 cc. of foul purulent sputum daily (fig. 1).

The drop to 30 cc. with intramuscular therapy and the disappearance of his symptoms after combined and then local therapy alone are shown. He has been working for twenty-one months and has had no recurrence of expectoration despite three episodes of coryza.

CASE 2.—The patient was a 30 year old woman in whom bronchiectasis had developed when she was 2 years old. The disease followed suppurative pneumonia complicating measles and pertussis. She had repeated attacks of pneumonia thereafter, and for the last fifteen years she had been confined to her home and had taken her meals in a room apart from her family because of the fetid sputum. The bronchogram showed that the lower lobes of both lungs and the middle lobe of the right lung were involved. Large sacculations were present. The patient was expectorating about 200 cc. of extremely fetid sputum (fig. 1). A sixteen day course of sulfadiazine reduced the amount of sputum to about 80 cc., but this remained fetid and purulent. Intramuscular injections of penicillin—15,000 units every three hours for one week—further reduced the amount of sputum to 40 cc. This also was purulent but was less odorous.

Fourteen daily intratracheal instillations of 50,000 units of penicillin dissolved in 50 cc of isotonic solution of sodium chloride were given bilaterally. The amount of sputum dropped to 30 cc., and for the first time the odor was abolished. The patient has been observed for seventeen months. Except for a rise in the volume of sputum to 60 and 90 cc. respectively following attacks of coryza one month and two months after treatment, the patient's sputum has stayed below 30 cc. in amount and has never since had an odor.

This was considered a good immediate result, and it was well maintained.

CASE 3.—The patient was a 63 year old man who was extremely ill when admitted to the hospital. He had fever and was much too weak for instillations. His illness dated back twenty-five years and had grown considerably worse in the last year and a half. His sputum was fetid and amounted to 240 cc. daily. A bronchogram made earlier showed extensive saccular bronchiectasis in the lower lobes of both lungs. There had been recent pneumonic extensions into the upper lobes. As figure 1 shows, he got relatively little benefit from combined intramuscular injections of penicillin and sulfonamide drugs but did well when there was added 50,000 units per cubic centimeter of nebulized penicillin four times a day.

The quantity of sputum dropped from 185 cc. to 65 cc. His fever subsided, and he felt stronger. The sputum was still purulent and odorous, and he was therefore given eight intratracheal instillations of 100,000 units in 20 cc. of isotonic solution of sodium chloride over a period of thirteen days. Under this therapy, the sputum lost its odor and became mucoid and the quantity decreased to 40 cc. a day. The patient was discharged much improved, and he returned to part time work. After one month, however, the sputum was again foul and amounted to 120 cc. daily. He entered his local hospital and died four months after the penicillin treatment had been terminated. The cause of death was failure of the right side of the heart and generalized amyloidosis.

In this instance there was a good immediate result, but recurrence took place within two months.

CASE 4.—A woman of 26 years was admitted for lobectomy. The lower lobe of her left lung was the seat of extensive sacculations. The bronchi of the lingula were slightly involved. She had a sizable reduction in amount of sputum during sulfonamide therapy (fig. 1), but within one week the sputum rose again to its original volume. With the patient under intramuscular penicillin therapy the level of sputum dropped to a daily average of 70 cc., and a further decrease to 50 cc.

followed intratracheal instillations. She left the hospital, and for the first two weeks the sputum was mucoid and odorless and the volume measured but 10 cc. Within a month, however, it became purulent and fetid and the amount climbed to 75·cc Another series of instillations reduced the volume by half, and then lobectomy with lingulectomy was performed, with cure. The excised lobe showed evidence of persisting bronchial infection.

The immediate response was fair, but there was a recurrence one month afterward.

CASE 5.—A 32 year old man was admitted for lobectomy. He had saccular bronchiectasis of the lower lobe of the left lung, dating back two and a half years, and was expectorating on the average of 100 cc. of fetid sputum (fig. 2). He was

Fig. 2 (cases 5 to 9).—Average volume of sputum in twenty-four hours under specified therapy administered successively.

submitted to bronchoscopy, and the bronchoscopist reported as follows: "A large quantity of foul, sanguinous, purulent material wells up from all branches of the lower lobe of the left lung. The mucosa is inflamed and bleeds easily." In preparation for lobectomy, the patient was given ten daily intratracheal instillations of 100,000 units of penicillin combined with 15,000 units every three hours intramuscularly.

After the sixth instillation there was no longer any cough or expectoration. Twenty-four hours after the ninth instillation bronchoscopy was performed again, and the bronchoscopist's findings were "small particles of nonodorous secretion clinging to the wall of the bronchus of the lower lobe of the left lung. There was no appearance of pus with cough. The mucous membrane was paler and did not bleed. This was a dramatic resolution of a suppurative process. There was

no odor and practically no secretion." Aerobic and anaerobic culture of the bronchoscopic secretions failed to reveal any growth. The patient remained asymptomatic, and the lobectomy was postponed. However, after a month the cough and expectoration returned, and the volume of sputum, again foul and purulent, measured 75 cc. The patient was given three more intrabronchial instillations in preparation for lobectomy, and by the day before the operation the level of sputum had decreased to 15 cc. The bronchi of the excised lobe contained little secretion. The operation resulted in a definitive cure.

Here was another excellent immediate result with a recurrence after one month followed by a satisfactory preoperative response.

CASE 6.—A woman of 33, with two lobes involved, had a drop in the level of sputum of less than 50 per cent after treatment (fig. 2). She suffered exacerbation of her symptoms, with spread of the disease three weeks after her discharge from the hospital. She is still considering surgical treatment.

The immediate and the late results were poor.

CASE 7.—The patient in this case had a fair immediate result, the amount of sputum dropping from 150 cc. to 50 cc. (fig. 2). Most of the decline occurred while the patient was receiving 100,000 units intramuscularly every six hours for nineteen days. Despite weekly intratracheal instillations of penicillin in the outpatient department, the volume of sputum returned almost to its original level after six weeks—a poor result.

CASE 8.—A 63 year old woman had symptoms for fifty years, with several acute exacerbations in the last year. On admission to the hospital her temperature was 102 F. Since she was too ill for intratracheal therapy, a nebulum of 50,000 units of penicillin dissolved in 1 cc. of isotonic solution of sodium chloride was given four times daily. During the first week the volume of sputum dropped from 90 cc. to 55 cc. (fig. 2). It remained at about that level during the second week of the inhalations. Her temperature became normal, and her strength increased. After eleven intratracheal instillations of 100,000 units of penicillin in 20 cc. of isotonic solution of sodium chloride, the amount of sputum decreased to 15 cc and it became mucoid. The patient has been observed for eleven months, and the amounts of sputum have remained at the same level.

The immediate and late results were good.

CASE 9.—The patient in this case also had a good immediate result—a drop in the level of sputum from 85 cc. daily to 15 cc. at the end of intratracheal treatment (fig. 2). He has been observed for eighteen months, and his daily volume of sputum has not exceeded 30 cc.—a fair late result.

CASES 10 and 11.—The patients in these cases had fair immediate results (fig. 3), which have been maintained for fifteen and eight months respectively.

CASES 12 and 13.—Nothing was gained from the therapy (fig. 3).

CASE 14.—This case is of particular interest. The patient was a 9 year old child who became ill with pertussis in the beginning of February 1945. Several weeks later she was found to have suppurative pneumonia and was admitted to a hospital for contagious diseases. The roentgenogram of her chest showed consolidation and atelectasis of the lower and middle lobes of the right lung. She was submitted to bronchoscopy twice, and large quantities of odorless pus were aspirated from the right bronchial tree. She was given a total of 2,640,000 units of penicillin intramuscularly and also a course of sulfonamide drugs during the next month, but without improvement.

In the ninth week of her illness she was transferred to the Mount Sinai Hospital. She still had fever and expectorated about 45 cc. of purulent sputum. On her admission to the hospital roentgenograms of her chest, taken on March 31, 1945, showed atelectasis of the lower and middle lobes of the right lung. Bronchoscopy was performed on April 6, and large quantities of odorless pus were aspirated from the bronchi of the lower and middle lobes of the right lung. Penicillin was given intramuscularly in doses of 20,000 units every three hours—altogether, 3,500,000 units over a twenty-three day period.

The fever subsided, and the amount of sputum dropped to about 15 cc. but was still purulent. On May 10 bronchoscopy was performed again and thick pus was aspirated from the same bronchi, but the secretions were not so profuse as they had been one month earlier. The physical signs of atelectasis persisted,
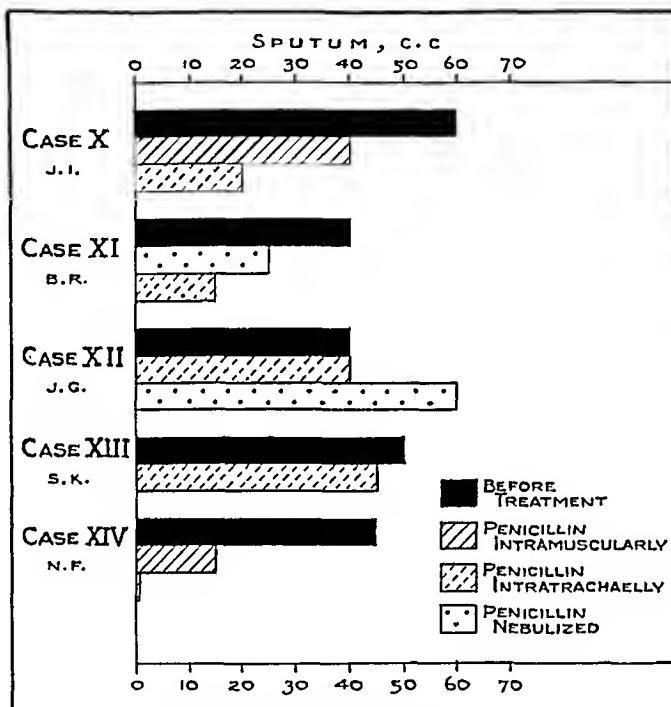
Fig. 3 (cases 10 to 14).—Average volume of sputum in twenty-four hours under specified therapy administered successively. The lowest bar in case 14 represents the volume of sputum under intratracheal therapy.

and a roentgenogram of the chest made one week after bronchscopy showed, on May 17, 1945 (fig. 4 A), that the lobes were still collapsed. The intramuscular injections of penicillin were resumed after bronchoscopy.

Because of the persistent atelectasis, a course of intratracheal penicillin therapy was started on May 22, 1946. By June 5 the patient had been given five instillations of 50,000 units in 10 cc. of isotonic solution of sodium chloride. After the third instillation the cough and expectoration disappeared.

A roentgenogram made on the day of the last instillation showed, for the first time in more than three months, partial reexpansion of the lobes (fig. 4 B). Eleven days later there was practically complete aeration of the involved lobes (fig. 4 C). Three months later a bronchogram of the lower and middle lobes of the right lung showed that she had not entirely escaped the sequelae of the suppurative pneumonia and atelectasis in spite of the normal-appearing roentgeno-

gram of the chest. There was slight cylindric dilatation of the anterolateral branch of the bronchus of the lower lobe of the right lung. She has now been observed for thirteen months, and there has been no recurrence of cough or expectoration in spite of two attacks of coryza.

RESULTS OF TREATMENT

Immediate results were considered excellent in 2 patients, both of whom had their disease for only two and one half years; good in 4 patients; fair in 4, and poor in 3. Thus 10 out of 13 patients experi-
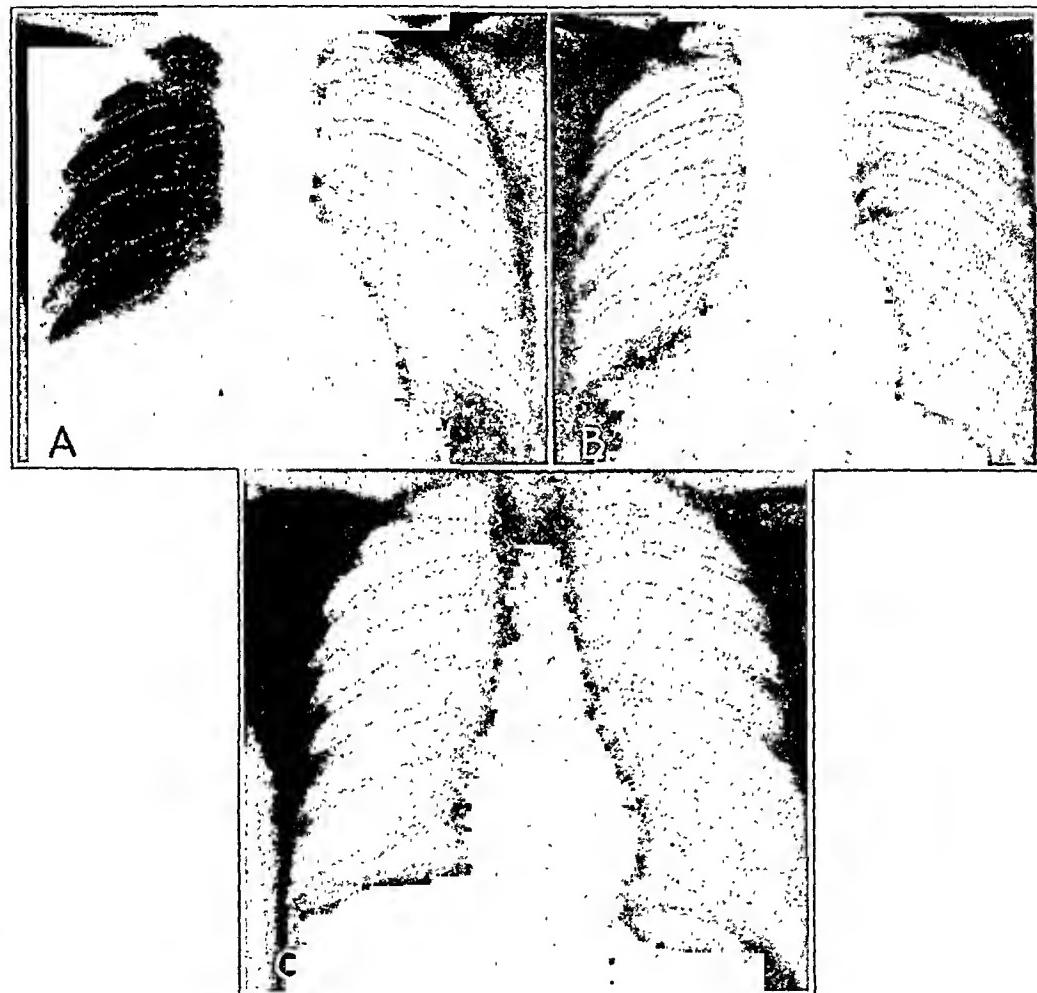
Fig. 4.—Roentgenograms of the chest of a 9 year old child with suppurative pneumonia and atelectasis following pertussis. *A,* roentgenogram of the chest before intratracheal penicillin therapy shows diffuse opacity in the lower field of the right lung, representing atelectasis of the lower and middle lobes. The appearance has been unchanged for more than three months. *B,* roentgenogram of the chest taken on the last day of intratracheal penicillin therapy, with beginning reexpansion of the previously unaerated lobes. *C,* eleven days later almost complete aeration of the affected lobes has occurred.

enced a drop in volume of sputum of 50 per cent or more immediately after treatment. Four of them had a recurrence of symptoms within two months. The 3 with poor immediate results remained in this

category. The later results were therefore as follows: excellent in 1, good in 2, fair in 3 and poor in 7.

It is to be remarked that of the 10 patients with a favorable immediate result the addition of intrabronchial or intratracheal administration of penicillin was accompanied in almost all by a reduction in the

TABLE 2.—*Immediate and Late Results of Treatment with Intratracheal Administration of Penicillin*

			Average 24 Hour Volume of Sputum, Cc.		Results of Treatment *		
Case	No. of Instilla- tions	Single Instillation Dosage, Units	Before Treat- ment	With Intra- tracheal Adminis- tration of Penicillin	Immediate	Late	Comment
1	11	10,000 to 25,000	150	None	Excel- lent	Excel- lent	No recurrence after 21 mo.; completely free of cough and expectoration
2	14	50,000	200	30	Good	Good	No significant recurrence in 17 mo.; sputum, 30 ec. or less; no odor
3	8	100,000	240	40	Good	Poor	Recurrence after 2 mo. and death from failure of the right side of the heart and amyloidosis in 4 mo.
4	12	37,500 to 75,000	135	50	Fair	Poor	Recurrence after 1 mo.; lobectomy and cure
5	10	100,000	100	15	Excel- lent†	Poor	No sputum at end of instil- lations; recurrence in 1 mo., with 75 ec. of fetid and purulent sputum; pre- operative instillations, with reduction to 15 ec., fol- lowed by lobectomy with cure
6	13	100,000	130	70	Poor	Poor	Exacerbation, with spread of disease in 3 wk.; no im- provement for next 6 mo.; patient awaiting lobec- tomy
7	12	100,000	150	50	Fair	Poor	Recurrence in 6 wk.; no im- provement for next year
8	11	100,000	90	15	Good	Good	No recurrence; sputum about 15 cc. for next 11 mo.
9	15	30,000 to 50,000	85	15	Good	Fair	No recurrence; sputum 30 cc. or less for next 18 mo.
10	12	50,000 to 100,000	60	20	Fair	Fair	No recurrence; sputum 25 cc. for next 15 mo.
11	10	200,000	40	15	Fair	Fair	No recurrence; sputum 15 cc. or less for next 8 mo.
12	13	200,000	40	40	Poor	Poor	Condition unimproved during the next 6 mo.
13	7	200,000	50	45	Poor	Poor	Condition unimproved during the next year

* Excellent indicates cessation of expectoration; good, reduction of sputum exceeding 80 per cent; fair, reduction of sputum 50 to 80 per cent, and poor, reduction of sputum less than 50 per cent.
† Expectoration ceased after the sixth instillation.

volume of sputum beyond that which had previously been effected by intramuscular injections of penicillin, nebulized penicillin or sulfonamide drugs. Moreover, the only 2 patients whose symptoms entirely disappeared immediately after treatment (cases 1 and 5) were both

given intratracheal and intramuscular therapy simultaneously. It may be noted further that 2 other patients with recent pneumonic spreads, who could not be given instillations initially, improved considerably with inhalations of nebulized penicillin (cases 3 and 8). Both these patients had further reductions of sputum with intratracheal instillations.

There are instances, however, in which nebulized penicillin apparently does not reach the affected portion of the bronchial tree. A recent experience with a patient not included in the present series illustrates this. The patient had suppurative saccular bronchiectasis of the middle lobe of the right lung and was being prepared for lobectomy. Bronchoscopy revealed large amounts of fetid pus pouring out of the bronchial orifice of the middle lobe of the right lung, which was considerably narrowed by swelling of the mucosa. A ten day course of nebulized penicillin, administered for fifteen minutes every hour for twelve hours daily, resulted in no change in the amount or the character of the sputum. However, five instillations of 100,000 units of penicillin dissolved in 10 cc. of isotonic solution of sodium chloride, given daily through a bronchoscope directly into the orifice of the middle lobe of the right lung, resulted in the complete disappearance of the secretions, and when the lobe was excised the dilated bronchi and their sacculations were found to be almost completely dry. At the present time some patients are being treated with a preliminary course of nebulized penicillin, and when the response is not entirely satisfactory a series of intratracheal instillations is prescribed.

The fair proportion of patients with a favorable immediate response would indicate that the combined intratracheal and intramuscular therapy may be a valuable adjunct in the preparation of patients for lobectomy. A drier and less infected bronchial tree should aid in the prevention of aspiration of pus into uninvolved pulmonary areas during and after surgical treatment. For patients not treated surgically the therapy as given holds out less, although some appear to obtain fairly lasting amelioration of symptoms. Obviously, instillations cannot be continued indefinitely. It remains to be seen by further study whether the incidence of recurrence can be lessened by prolonged administration of nebulized penicillin or by the addition of other antibiotic and chemotherapeutic agents.

The single experience with atelectasis complicating suppurative pneumonia—the forerunner of bronchiectasis—suggests that intratracheal instillations may be a useful addition to the present methods of therapy. Further trial of the method in the important area of the prevention of bronchiectasis is in progress.

SUMMARY

1. Thirteen patients with chronic suppurative bronchiectasis and 1 patient with suppurative pneumonia, atelectasis and early bronchiec-

2. Ten of the 13 patients with chronic bronchiectasis had a drop of 50 per cent or more in the volume of sputum in twenty-four hours following the instillations. In each case the instillations held the volume of sputum at a lower level than could be maintained previously with the use of sulfonamide drugs, intramuscular injections of penicillin or nebulized penicillin. Three patients had no significant reduction of sputum after the instillations.

3. Recurrence of symptoms was experienced by 4 patients with a favorable immediate response. All recurrences took place within two months.   •

4. Intratracheal penicillin therapy appears to be a useful adjunct in the preparation of patients for lobectomy. It reduces the volume of sputum, renders it less purulent and abolishes the odor.

5. Some patients unsuitable for surgical intervention obtain fairly lasting ameliorative effects from the therapy.

6. One patient with suppurative pneumonia and atelectasis of more than three months' duration experienced immediate and lasting clearing and reexpansion of two lobes after intratracheal instillation.

1097 Madison Avenue.

News and Comment

Annual Meeting of American Psychiatric Association.—The one hundred and third annual meeting of the American Psychiatric Association will be held in New York, May 19 to 23, at the Pennsylvania Hotel. The association was founded in 1883 and is the oldest body of medical specialists in the country. It has over 3,500 members in the United States, Canada, Latin America and Europe.

The program consists in one hundred and twenty papers reporting on advances in such diverse fields as child psychiatry, brain surgery, convulsive disorders, shock therapy, alcoholism and forensic psychiatry. Leaders in the Veterans Administration will meet on Wednesday morning.

The program includes: a symposium on the treatment of the hospitalized neuropsychiatric patient; a discussion on motivation in recovery from medical and psychiatric illnesses; reports on physiologic and clinical rationale of the new brief stimulus therapy and on a study of the effect which electric shock therapy has on mental functions; a clinical evaluation of electronarcosis therapy in comparison with electroshock therapy, and the part psychiatry plays in the administration of justice. On Wednesday afternoon there will be a presentation on the recently organized nonprofit Psychiatric Foundation and its role in public education and on the role of psychiatry in the world today. On Thursday afternoon papers will be presented on the experiences and implications of psychiatry in World War II; reports will be presented on two hundred lobotomies performed on patients with diverse psychiatric conditions, and there will be reports on outpatient treatment of persons with chronic alcoholism, penicillin therapy in dementia paralytica and the use of ergotamine compounds in the treatment of simple anxiety states. On Thursday evening a round table dinner discussion will be held on the program of the United States Public Health Service for the development of training, research and community service in mental health, as well as discussions on the role of social agencies in dealing with constitutional psychopaths and the importance of psychophysiologic interrelationships.

On Friday afternoon a report will be presented on an experiment in group psychotherapy of patients for whom interpersonal difficulties in the home appeared noxious.

Further information may be procured by writing to the secretary-treasurer of the American Psychiatric Association, Dr. Leo H. Bartemeier, 3044 West Grand Boulevard, Detroit.

Book Reviews

The Diagnosis and Treatment of Pulmonary Tuberculosis. By Moses J. Stone, M.D., and Paul Dufault, M.D. Price, $3.50. Pp. 325, with 93 illustrations. Philadelphia: Lea & Febiger, 1946.

This small volume is remarkable because so much sound information on pulmonary tuberculosis has been condensed into such little space. By the elimination of illustrations, blank pages and bibliography there is only a little more than 200 pages of text; yet practically every field of pulmonary tuberculosis has been clearly, if but briefly, discussed. The authors' claim that "brevity is the byword" is obviously substantiated. Nevertheless, the work is a good textbook and not a compendium. Naturally, such condensation is not to be expected in any work meant for research workers or specialists; the authors state that it is for "students, teachers and all physicians desiring a practical knowledge of the disease." Even for the most highly trained, however, it affords a refreshing review of the important phases of tuberculosis without any "dissertations and controversies."

One of the outstanding educational features is the attempt to correlate clinical and roentgenologic observations with good illustrations of the pathologic changes. There is also a modernization of clinical methods, especially methods of physical examination, with an excellent appraisal of values. Obsolete procedures (such as measuring the Krönig isthmus) are put in the "historical museum," but the necessity of a thorough study of the human being by the taking of the history, inspection, palpation, percussion and auscultation still exists in spite of the far greater usefulness of roentgen rays, because the "x-ray may not always be available." This reviewer would also suggest that methods other than roentgenologic provide "added knowledge of the patient, which x-rays and laboratory cannot give." Differential diagnosis, various complications, methods of treatment, after-care and rehabilitation are generally well covered.

In view of the attempt to arrive at a happy medium between brevity and a mass of facts, the product must be expected to have something lacking. It is hoped that the following remarks may be considered as suggestions rather than as criticisms, and that the authors may be able to effect certain changes in future editions.

In spite of studied intentions, certain controversies are unavoidably encountered, because their elimination would emasculate any work on diseases of the chest. The views on allergy and immunity, the protection afforded by the primary infections, the question of cancer of the lung versus cancer of the bronchi and indications for the many forms of treatment are by no means closed chapters. What was meant to be eliminated, no doubt, are bygone historic differences of opinion which now add romance and make the subject attractive for the medical historians and research workers.

The differential diagnosis, although rather good, still lacks the mention of some important conditions, such as lipid pneumonia; chronic streptococcic, staphylococcic and Friedländer pneumonia; massive collapse; infarction; passive congestion from cardiac disease; atopic asthma, and malformations. There should be a paragraph on emphysema, because of its pathogenesis and its frequent presence as a diagnostic problem in diseases of the chest. The paragraphs on industrial disease do not include siderosis; the discussion on tumors might well include dermoids, fibromas, neurofibromas, mesotheliomas and tumors of the cord and body wall which encroach on the pleura or the pulmonary structures. The fifty or more other diseases are of course too uncommon to merit consideration in such a limited text.

More emphasis might well be given the complex diagnostic problem of concomitant and associated disease. In addition to diabetes, syphilis and silicosis,

cancer of the lungs, bronchiectasis, asthma and the whole gamut of diseases of the lungs could well be cited as occasionally complicating the diagnosis and treatment of tuberculosis. Furthermore, the association of mental disease and tuberculosis is almost a specialty of its own.

In the discussion of management of sanatoriums the different problems arising in the home; in private, public and veterans' hospitals, and especially in mental institutions might have been mentioned to advantage. The importance of nursing care and esthetic environment are perhaps underemphasized.

One error of calculation appears on page 203, where cases involving pneumothorax are said to be 0.4 per cent of all cases cited, whereas the figure should be about 4.5 per cent.

Regarding the "unknown cause" of psittacosis, there seems to be little doubt now that it is of virus nature.

The bibliography does not appear to contain the most representative references, but the illustrations are exceptionally well chosen, of the highest grade and are well reproduced. The format, paper, binding, print and publishing are beyond criticism.

This book is highly recommended for undergraduates as perhaps the best modern text in English for classroom work. It is also good for the book shelf of every physician.

Publicaciones del Centro de Investigaciones Tisiologicas. Edited by Prof. Roque A. Izzo, Director. Vol. IX. Buenos Aires, Argentina: Pabellon "Las Provincias," Hospital Tornu, 1945.

The ninth collection of papers of "Del Centro," under Professor Izzo's direction, contains some valuable contributions.

The first article, on the roentgenologic exploration of the hearts in a group of 23 cases of mitral stenosis in adults by Laplace, is especially good. In addition to the standard measurements, the author describes how other signs may be of great usefulness. By a discussion of the skilful application of fluoroscopy and exposures at a distance of 2 meters (teleroentgenograms) on both anterior-posterior and oblique views, the author brings out some refined methods of detecting the progressive stages of mitral stricture.

The study is divided into sections on the heart and its borders, the mediastinum and the pulmonary fields around the heart. The cardiac changes are more or less progressive in a definite order. With regard to the anterior-posterior view, the author describes first the left border of the heart. Two types ae recognizable, viz., the early type, in which the region of the pulmonary conus becomes flattened and the angle between the left ventricle and pulmonary artery obliterated (47.8 per cent of the cases), and the advanced type, with varying degrees of expansion outward from the region of the conus (52.2 per cent of his cases). The fine differentiation of the left auricular appendage (which is fixed) from the pulmonary artery (which pulsates) is intriguing but seems academic or only for the most highly skilled observer.

The right border of the heart also passes through several stages of involvement following or overlapping those on the left, characterized at first by an incursion of the left auricle into the field, eclipsing partially the upper right auricle and apparently the aortic-auricular junction. Later the right auricle enlarges, and at the same time it rotates the heart around the axis toward the left. As a consequence, there is frequently the double image originating at the aortic-auricular junction and separating downward. The elevation and lengthening of the auricular arc were present in 96 per cent of the cases studied, but the "double arc" phenomenon was present only in 26 per cent of the cases. All 23 cases showed various combinations of the described phenomena. Cossio's sign of "dancing bronchi" is mentioned, but it is probably due to "dancing" blood vessel columns.

The mediastinal phenomena are, first, the clinical phenomenon (Ortner's sign, i. e. partial paralysis of the recurrent laryngeal nerve) ; the esophageal phenomenon, and the tracheobronchial phenomenon. The esophageal phenomenon is shown best

on an oblique view when a thick barium meal is used. There is a decided slowing of passage of the barium, a widening of the esophageal shadow, indentations of the shadow in the auricular region and pulsations transmitted to the barium mixture. The tracheobronchial phenomenon is a widening of the angle of the main bronchi at the hilus to over 77 degrees and a lifting and arching of the left main bronchus, demonstrated by a small instillation of iodized oil. On the oblique view of the left side the auricle salient as well as an irregular narrowing of esophageal shadows is present. The shadows in the pulmonary field are too well known to require comment.

In a study of brain metastases in cancers of the lung, Hernandez and Irogoyen found that 8 per cent of 50 patients had such metastases, which were recognized clinically, and that pulmonary symptoms always preceded cerebral symptoms.

Aguilar and Sirlin studied the so-called round infiltrates (Wartenhorst-Albert foci). The authors correctly state that the designation is ill advised. There are many varieties of pathologic conditions, from thinly encapsulated to heavily encapsulated caseous infiltrations. Some are calcified, some become resorbed and some excavate. They may be part of a primary infection, the "precocious type of Redeker" or "evolutive budding" type. The role of the bronchi, constitution, immunity and reaction of local tissue are discussed. The differential diagnosis is thoroughly given. It is concluded that although "round infiltrates" are generally quiescent foci they may be reactivated to disease. In spite of the similar appearance in the roentgenogram, they are not an "independent nosologic process."

Meccheri thoroughly studied venous pressure in normal and many pathologic conditions. The cause of high pressures is primarily cardiac insufficiency or local interference with circulation. Serial readings have some prognostic value in determination of trends in cardiac function. They may be used to differentiate edemas, cyanosis, enlargement of the liver and other conditions of noncardiac origin.

Other reports are of less practical value, but nearly all reflect a high order of work.

Medical Education and the Changing Order: Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. By Raymond B. Allen, M.D., Ph.D. Price, $1.50. Pp. 142. New York: The Commonwealth Fund, 1946.

In this readable little volume Dr. Allen, president-elect of the University of Washington, presents his views of what should constitute a medical education. The discussion is from the point of view of his extensive experience as dean of the schools of medicine, pharmacy and dentistry of the University of Illinois.

The first need in medical education is to bring together good teachers and good students. The environment ought to be conducive to developments which reflect not alone the scientific but also the cultural, social and economic aspects of society With the community losing its complacency about poverty, industrial unrest and social deficiencies generally, more is demanded of the physician and of the medical education which must prepare him for this broader field. Physicians always will be occupied in replacing the damage caused by disease and maladjustments, but preventive medicine will occupy a larger part of his attention in the future, which means that he must be a broadly informed and cultured person to command the respect of leaders in the many phases of human activity of the changing order. The medical profession otherwise is likely to degenerate to the level of a trade.

Medical education, Dr. Allen believes, shares in the responsibility for the failure of the medical profession to exhibit social insight and exert sufficiently aggressive leadership in developing procedure for better distribution of the expanding technology of medicine. The gap in medicine between the "know how" and the "doing" for the benefit of all the people can be closed only by physicians who have social as well as technical training. Medicine has been concerned so long, so intensively and so successfully with ill health and disease that it has occupied itself too little

with the subject of good health. Medical education should stimulate the building of this superstructure to meet fully the needs of the times in regard to health.

Of graduate medical education, Dr. Allen implies that provision of experience in research is essential for a truly graduate university discipline. Programs falling short in this requirement are merely training for proficiency, and, important though this training is, no one ought to be misled into regarding the clinical specialist as a scientist. The library, the various conferences and the seminars all serve educational objectives. A well run graduate program provides these facilities in abundance. Standards of licensure and certification are important, but medical education ought to be concerned primarily with the development of the highest possible standards of learning and performance of which the student, intern, graduate student or practicing physician is capable.

The recruiting of good candidates for a medical education is a responsibility which physicians ought to take more seriously. Physicians know more about the family background and aptitudes of the young persons of their acquaintance than is possible perhaps for any one else to know; yet few physicians do much about encouraging gifted youths to study medicine. Medicine needs both scientifically and socially minded people, and the prospective student should be one who has tolerance, kindness, friendliness, dependability, industry, integrity, honesty, courage and determination. There is no room for any other kind, because medical schools are interested in producing only good physicians.

A physician should be sensitive to the values of beauty, goodness and wisdom as these values are conveyed by the creative arts and religion. And if medicine is to progress as a social as well as a biologic science, it must broaden its outlook and adjust its educational program. To bring premedical and medical curriculums up to date, one must recognize the fact that medicine has outgrown the limitations of the laboratory and the clinic. Pertinent phases of the disciplines of the social sciences and humanities should be among required studies.

These and the many other challenging conclusions of the author make this book worth reading by all intelligent persons, be they laymen or physicians. For those involved in medical education the book should be required reading.

The Duodenal Glands of Brunner in Man, Their Distribution and Quantity: An Anatomical Study. By Erik Landboe-Christensen. Price, 20 kroner. Copenhagen: Ejnar Munksgaard, 1944. London: Humphrey Milford, Oxford University Press, 1946.

This is a detailed anatomic investigation of the location, arrangement and quantity of the duodenal glands of Brunner in man, based on the observations in 53 cadavers of all age classes examined by a gross staining technic. By direct observation of the stained duodenums in surface view and, after they were embedded in gelatin, in profile section, the author has elucidated the topography of the glands and has estimated the quantitative glandular density throughout the area. Histologic details other than the form of the glands and glandular islands have not been considered. Extensive descriptions accompanied with maps showing the extent of the area of the Brunner glands and the density of glandular distribution are given for each individual specimen.

The author has found that proximally the area of the Brunner glands borders along the pyloric ring, on which it gradually encroaches and frequently crosses with advancing age. The distal delimitation was shown to be less definite: in five sixths of the cases isolated islands of glandular tissue were discovered to extend to a point midway between the inferior duodenal papilla and the commencement of the jejunum. In nearly two thirds of the cases Brunner glands were found to extend down as far as 4.5 cm. into the jejunum. In 6 of the 53 cases the most distal glands were present at the level of the inferior duodenal papilla. The density of the glandular tissue was found to be subject to a high degree of variation between individual specimens; in general, the acinar substance is densest proximally and gradually decreases to isolated glandular islands distally. The relative density was shown to be greatest in youth and the absolute density greatest in

middle age. There is a gradual reduction of the total glandular substance with advancing years. The author observed that the density is usually least on the wall facing the pancreas.

The frequency of pathologic changes in adjacent structures being considered, surprisingly little attention has been paid to the duodenum by physiologists and anatomists until recently, slight importance being attached to this viscus in relation to allied clinical pathologic conditions. Currently, however, the organ is being studied more and more, and a comprehensive investigation of one of the major components of the duodenum, such as is here presented, is therefore timely.

Medical Clinics of North America. Boston Number: Symposium on Specific Methods of Treatment. Pp. 244. Philadelphia: W. B. Saunders Company, 1946.

This symposium on therapy brings the internist and general practitioner up to date on a variety of interesting and timely subjects. The field is not limited to purely medical problems alone, for it includes discussions on general surgery, otolaryngology, gynecology and urology from the medical viewpoint. Of particular interest is the article entitled "Medical Aspects of Renal Insufficiency in Urologic Practice" After the pathologic physiology of urinary obstruction, urinary infection and certain functional abnormalities of renal blood flow are discussed, the diagnostic procedures and therapy are presented, outstanding both in clarity and in physiologic approach.

Several of the purely medical articles offer nothing more than a brief review of well known and clinically proved diagnostic and therapeutic measures. Special mention should be made, however, of the thorough and enlightening presentations of the viral diseases, the anemias and diabetic coma. A clinical appraisal of streptomycin, Demerol (1-methyl-4-phenyl piperidine 4-carbonic acid), Benadryl (beta-dimethylaminoethyl benzhydryl ether hydrochloride) and Pyribenzamine (N'pyridil-N'benzyl-N-dimethylethylenediamine) is submitted. Psychosomatic medicine is given a place in the consideration of obesity and neurocirculatory asthenia. Finally, an extremely stimulating clinicopathologic conference on amyloid kidney brings this uncommonly recognized disease to mind.

As a whole, the articles are well chosen and well presented, but the reviewer would like to have seen discussions of the more recent advances in hyperthyroid and diabetic therapy.

Om strumaproblemet paa grundlag af en undersøgelse i tre danske landsogne (The Goiter Problem Elucidated Through Studies in Three Rural Districts in Denmark). By Knud Rosenquist. Pp. 389. Copenhagen: Ejnar Munksgaard, 1943.

This rather lengthy monograph deals with an extremely careful, thorough and intelligent investigation of the incidence of endemic goiter among the rural population of Denmark. As studies elsewhere have also shown, areas with a high incidence of goiter were found to have little iodine in the drinking water. The finding of similarly low iodine content in the drinking water of districts without particularly high incidence of goiter suggests the existence of other factors in the production of goiter than lack of iodine alone. The monograph is in Danish, but there is an excellent English summary by Dr. Hans Andersen.

Syndrome cortico-pleural: son étude clinique et expérimentale. By J. Skladal. Price, 160 fr. Pp. 144. Paris: Masson & Cie, 1946.

Skladal presents some of the more important clinical manifestations of the "corticopleural" syndrome which follows chronic pleural inflammation with fibrosis. The clinical discussions are supplemented by theoretic and experimental considerations. Many good roentgenograms are presented. This is an interesting monograph which should be of value to internists, phthisiologists and physiologists.

CEREBRAL MANIFESTATIONS OF ACUTE RHEUMATIC FEVER

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ACUTE rheumatic fever is well recognized as a cause of inflammation of the endocardium, the pericardial and pleural cavities, the joints and, occasionally, the lungs. In the brain, Sydenham's chorea is accepted as a rheumatic equivalent and a frequent cause of valvular lesions of the heart.[1] It is also fairly well known that Sydenham's chorea may account for a great variety of behavior disorders in children.[2] However, it is not so well known that acute rheumatic fever may produce severe mental changes of a different character and without the motor phenomena typical of Sydenham's chorea. It is this group with which our report is concerned. In some of these patients the disturbance is bizarre, with vague hallucinations, phobias and acute panic-like episodes. Delirium, with increased psychomotor activity, restlessness, twitching of the muscles and even convulsions may appear. In some cases the cataleptic features may be prominent, so that the entire picture resembles schizophrenia. In fact, those who look on schizophrenia as a type of reaction for which there may be a variety of causes, both constitutional and acquired, consider that rheumatic encephalitis is the cause in some cases of so-called schizophrenia. Bruetsch[3] found that 6.4 per cent of a group of patients dying in a hospital for patients with mental diseases showed evidence of endocarditis at autopsy. The age of the lesions varied from a few days to over thirty years. In the functional group, those with dementia precox or manic-depressive or involutional psychoses, 8.1 per cent showed endocarditis at autopsy. Only 1 per cent of the patients with dementia paralytica showed such changes. Bruetsch described anatomic changes in the brain which he believed were a result of rheumatic endarteritis.

1. Greenfield, J. G., and Wolfsohn, J. M.: The Pathology of Sydenham's Chorea, Lancet **2**:603-606 (Sept. 16) 1922. Waggoner, R. W.: Sydenham's Chorea, Am. J. M. Sc. **182**:467-476 (Oct.) 1931.

2. Neal, J. B.: Encephalitis: A Clinical Study, New York, Grune & Stratton, Inc., 1942.

3. Bruetsch, W. L.: The Histopathology of Psychoses with Subacute Bacterial and Chronic Verrucose Rheumatic Endocarditis, Am. J. Psychiat. **95**:335-346 (Sept.) 1938.

He was of the opinion that acute rheumatic fever can cause diffuse damage to the brain and can give rise to a psychosis, usually of the schizophrenic type. His experience has been more with the late effects and not with the acute episodes during the active rheumatic inflammation. In 1942 Foster[4] reported a study of the association between convulsive seizures and rheumatic cardiac disease. · The incidence was two and a half to seven times more frequent among a group of 2,153 patients with rheumatic cardiac disease than among the general population. Bruetsch[5] has reported 3 cases of convulsions in which the patients showed endarteritis in the brain at autopsy, which he considered of rheumatic origin.

Sacks[6] has reviewed the pathologic changes of rheumatic fever and emphasized the widespread involvement of the peripheral arteries. The small arteries, those of medium caliber, the arterioles and the sinusoidal capillaries are most frequently involved. In chorea, he described a diffuse encephalitis or meningoencephalitis with the main lesions in and about the blood vessels. Winkelman and Eckel[7] have described meningoencephalitis in acute rheumatic fever. They stressed the importance of the edema. There is endarteritis of the small vessels, with areas of incomplete softening; acellular areas in the cortex are a prominent feature. The neuropathologic picture is complicated by embolic phenomena when there is endocarditis. In addition to endarteritis and lysis of the nerve cells, there is the usual reactive phenomena to degeneration, that is, a glial mesodermal reaction. They pointed out that it is not a specific lesion. The changes are similar to those occurring in other acute infections, toxemias and anoxemias.[8] Bruetsch[9] found involvement of the small blood vessels, usually limited to the cortex. There was intimal proliferation, with small or large areas of infarction. Numerous acellular areas were found. He stated that the basic lesion is a chronic vascular process of an endarteritic type. Kernohan, Wolt-

4. Foster, D. B.: Association Between Convulsive Seizures and Rheumatic Heart Disease, Arch. Neurol. & Psychiat. **47**:254-264 (Feb.) 1942.

5. Bruetsch, W. L.: Rheumatic Epilepsy: Sequel of Rheumatic Fever, Am. J. Psychiat. **98**:727-732 (March) 1942.

6. Sacks, B.: The Pathology of Rheumatic Fever: A Critical Review, Am. Heart J. **1**:750-772 (Aug.) 1926.

7. Winkelman, N. W., and Eckel, J. L.: Endarteritis of the Small Cortical Vessels in Severe Infections and Toxemias, Arch. Neurol. & Psychiat. **21**:863-875 (April) 1929; The Brain in Acute Rheumatic Fever: Nonsuppurative Meningo-Encephalitis Rheumatica, ibid. **28**:844-870 (Oct.) 1932.

8. Chornyak, J.: The Structural Changes Produced in the Human Brain by Oxygen Deprivation (Anoxemia) and Their Pathogenesis, Ann Arbor, Mich., Edwards Bros., Inc., 1938.

9. Bruetsch, W. L.: Chronic Rheumatic Brain Disease as a Possible Factor in the Causation of Some Cases of Dementia Praecox, Am. J. Psychiat. **97**:276-296 (Sept.) 1940; footnote 3.

man and Barnes [10] concluded from a pathologic study of 42 cases that changes in the central nervous system, with or without symptoms, not only were common with all types of endocarditis but also were as distinctive as the various types of endocarditis and could be correlated one with the other. They stated that more careful neurologic and psychiatric studies of patients would probably show a greater incidence of symptoms than is now appreciated.

There has been little discussion of these acute mental changes in patients with rheumatic fever in recent years. Kernohan, Woltman and Barnes [10] stated that in the middle of the nineteenth century cerebral involvement occurred in about 4.8 per cent of all cases of acute articular rheumatism and usually was fatal. Many of these patients died with hyperpyrexia, a serious complication of rheumatic fever. These authors reported 26 cases of rheumatic endocarditis studied at autopsy in which 96 per cent had pathologic changes in the brain. Twenty-one had some type of neuropsychiatric disturbance, most frequently hemiplegia (10 cases). Seven had headache, 5 had had convulsions and 3 had had chorea. Some type of mental abnormality developed in 5 during observation. Frisch [11] reported the history of an 11 year old girl with acute rheumatic fever in whom severe cerebral involvement developed, with hyperpyrexia and maniacal delirium. The spinal fluid showed an increase in cells and protein content. Therapy with solution of tribromoethanol was used during the stage of the acute symptoms, and after a prolonged course recovery occurred. Dobbs and de Saram [12] reported the case of an 8 year old girl in whom delirium, hyperventilation and then hyperpyrexia developed, followed by death, after acute rheumatic arthritis. Salicylate intoxication was suspected, but therapy with sodium bicarbonate had no effect. Postmortem examination showed many small hemorrhages throughout the white substance of the cerebellum, cerebrum and pons. Haskell [13] reported 2 cases, in 1914, of acute mental disturbances in rheumatic fever. One patient recovered in four months and 1 in seven months.

It is apparent that acute rheumatic fever may produce cerebral involvement different from the usual picture seen in Sydenham's chorea. The recent emphasis by Bruetsch on the end results of such lesions

10. Kernohan, J. W.; Woltman, H. W., and Barnes, A. R.: Involvement of the Nervous System Associated with Endocarditis: Neuropsychiatric and Neuropathologic Observations in Forty-Two Cases of Fatal Outcome, Arch. Neurol. & Psychiat. **42**:789-809 (Nov.) 1939.

11. Frisch, I. A.: Rheumatic Encephalitis (Chorea Insaniens): A Case Report with the Use of Avertin Therapy, J. Pediat. **5**:654-658 (Nov.) 1934.

12. Dobbs, R. H., and de Saram, G. S. W.: Acute Hemorrhagic Encephalitis Associated with Acute Rheumatism, J. Path. & Bact. **46**:437-440 (May) 1938.

13. Haskell, R. H.: Mental Disturbances Associated with Acute Articular Rheumatism, Am. J. Insan. **71**:361-381, 1914.

prompted us to study our cases carefully to determine the type and incidence of mental changes seen during the acute disease. The purpose of this paper is to describe the mental phenomena and behavior disorders observed in 207 cases of acute rheumatic fever.

REPORT OF CASES

Case 1.—A 22 year old white man was admitted to the hospital on April 12, 1944, with scarlet fever. The father was living and well. The mother died at 45 of unknown causes. One brother and one sister were living and well. His past history revealed a vague illness diagnosed as chorea at the age of 9. Careful questioning of the father did not suggest that this illness was true Sydenham's chorea. Seven months before this admission he had been studied in this hospital with exudative laryngitis.

He had become ill the day before his admission to the hospital with sore throat, chills and fever. A scarlatiniform rash appeared on the day of admission. Physical examination showed the typical cutaneous eruption of scarlet fever. The throat was red and swollen. The heart was normal, with no murmurs. The blood pressure was 100 systolic and 65 diastolic.

Culture of material from the throat on admission showed beta hemolytic streptococci, which were still present nine days later. The red blood cell count was 5,140,000, the hemoglobin content 65 per cent and the white blood cell count 8,100, with 78 per cent neutrophils, 18 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. The urine was normal.

He was given convalescent scarlet fever serum, 35 cc. on admission and 30 cc. on the thirteenth day in the hospital. He was only moderately uncomfortable and responded quickly to treatment.

On the seventeenth day in the hospital his temperature rose to 100 F., and it reached this level on the eighteenth, nineteenth and twentieth days. During this time he complained of a mild sore throat and severe headache. A culture from the throat failed to show hemolytic streptococci. The sedimentation rate on the twenty-first day was 31 mm. per hour (Westergren), and on the thirty-seventh day it was 57 mm. per hour. An electrocardiogram on the twenty-fourth day was within normal limits, with a rate of 75 and a P-R interval of 0.19 second. On the twenty-ninth day the P-R interval was 0.16, with a rate of 85.

On the forty-fifth day in the hospital he complained that the other patients were talking about him. He asked repeatedly for his father and insisted he could hear him talking in the hall. He was disoriented and agitated. The sedimentation rate had risen to 59 mm. per hour, and he complained of vague pain in the shoulders. The following day he was depressed and crying. He stated that he saw strange objects moving about his room and heard odd noises. Neurologic examination revealed no abnormalities. There were no cardiac murmurs. The blood pressure was 150 systolic and 70 diastolic and the pulse rate 144. Spinal puncture showed an initial pressure of 210 mm. of water, with normal dynamics. The spinal fluid was clear, with 2 white blood cells per cubic centimeter; the sugar content was 88 mg. per hundred cubic centimeters; total protein content was 65 Gm. per hundred cubic centimeters, and the colloidal gold curve was 4333220000. Reaction to a Wassermann test was negative.

He was fed with difficulty, as he thought the food had been poisoned, and he refused to take medication. On the forty-seventh day and for six days he was given 10 Gm. of sodium salicylate in 1,000 cc. of isotonic solution of sodium chloride intravenously. There was no perceptible improvement in his condition.

He varied from periods of quiet to periods of extreme hyperactivity. The sedimentation rate was 77 mm. per hour on the fiftieth day and 93 mm. per hour three days later.

He was extremely restless and slept only at short intervals. On the evening of the fifty-first day he seemed exhausted. The pulse rate was 170. The following morning he was much quieter. Cardiac examination, which had revealed no murmurs previously, now showed a blowing diastolic murmur along the left sternal border both when he was sitting erect and when he was lying down. At the apex was a grade 2 systolic murmur. The blood pressure was 135 systolic and 58 diastolic. There were no petechiae. The aortic diastolic murmur was heard throughout the remainder of his stay in the hospital. A second spinal puncture was done on the fifty-third day, which showed an initial pressure of 140 mm. of water, with normal dynamics. The fluid was clear, with 1 white blood cell per cubic centimeter; the sugar content was 180 mg. per hundred cubic centimeters; the protein content was 65 Gm. per hundred cubic centimeters; the colloidal gold curve was 2321100000, and reaction to the Wassermann test was negative. Cultures of the blood taken on the fifty-second and fifty-third days showed no growth. On the sixtieth day the sedimentation rate was 60 mm. per hour, on the sixty-seventh day it was 22 mm. per hour and on the seventy-first day it had dropped to normal.

With the onset of the delirium on the forty-sixth day the patient rapidly became maniacal and extremely difficult to control. During the forty-seventh day he wandered out of his room and was returned with difficulty. He was noisy and shouted for his father, saying he was going to die. During the night he pushed the ward boy out of his room and barricaded the door with his bed. After much persuasion he opened the door and went quietly to bed. During the night he moaned and mumbled to himself. The next day he had periods when he would sit quietly on the bed, looking out the window and refusing to talk. At other times he would become extremely restless, whistling, talking and calling for his father and attempting to get out of his room. On the fifty-second day he was notably active and difficult to control. He kept getting in and out of bed. He stated: "I am insane, but I won't plead insanity." He was fed with difficulty because he felt that the food was poisoned. On the fifty-fifth day he voided in his bed. By the fifty-seventh day he was much quieter and more easily managed. He would lie on his bed for hours not talking. He was sleeping better at night. He continued to complain of hearing odd noises and of hearing the voices of his father and brother. On the sixty-fifth day he complained that he was "imagining" things again. He "wanted to die" and stated that he knew he was "crazy." By the seventieth day he was spending most of his time in his room reading. He did not associate with the other men in the ward and appeared depressed and morose. He would eat only with urging. On the seventy-seventh day he told a patient that "he would be found hanging from a pipe," and that evening he started a fire with papers in his room. On the eighty-third day he expressed concern over his difficulty in writing and conveying his ideas.

The following are excerpts from a neuropsychiatric interview on the one hundred and eleventh day.

". . . When the boys were GI'ing this morning I just sat there instead of going in. I know I am in the wrong, but I lie around instead of helping out. I feel as though I ache. It seems like people are against me. From my actions I don't blame them a bit. The boys on the ward are against me because I know I don't deserve the service I have been getting. When the nurse asked me to come over here I hesitated to move. I just hate to be begged. I felt as though I had come to

fear that there wasn't much I can do about it. I just felt that the only way out was suicide. I hate to say it, but. . . .

"I feel that people think I am crazy or know I am, just by my actions, by not having a good time and not enjoying myself. I don't remember much about the first part of my illness. I remember being on ward 201 (closed ward). (Do you have that feeling about seeing your father and brother, imagining you see them?)' I don't do that any more. When I see them I know they are there. At times I think I will never get out of the hospital, Sir. (Do you feel mentally different now than before you became sick?) I noticed I was a little more cheerful the other day. I felt as though I could go to work. I hesitate, I just haven't got confidence in myself.· . . . I believe that is what it amounts to.

"I seem to be psychic as though some one is watching my every move. It seems to be more confusing all the time. I just think I don't have a chance any more. I feel that I am not wanted any more, being as filthy as I am. I just don't take care
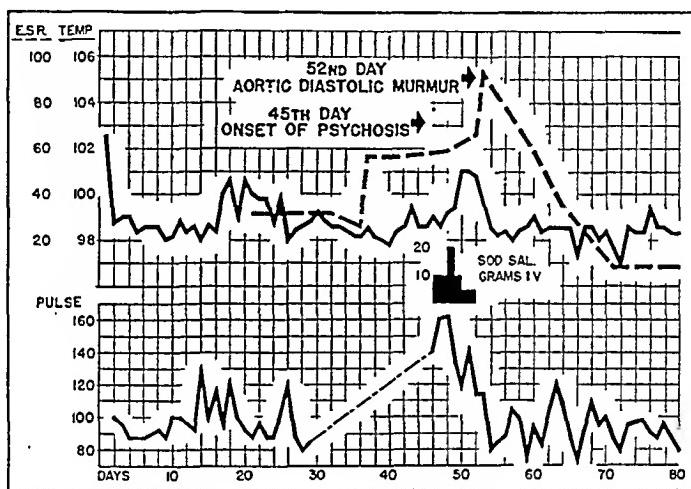
The course of the disease in the patient in case 1; aged 22, from his admission to the hospital with scarlet fever. The continuous line indicates the temperature, and the broken line indicates the sedimentation rate.

of myself any more. I don't take a shower and things like that. It seems as though I hear people talking about me. They seem to be saying that I am gold bricking, and it seems as though they are teasing me all the time. I hear the voices in the ward. I can't hear them now. It seems so real. When I am talking to the persons themselves they don't seem to be saying it, but when I turn my head or something it seems like I can hear it from the person I was just talking to. They either swear or say I should be down in 201 or Section 8 and that kind of stuff. The voices seem to accuse me of being lazy. I actually believe these occur, I guess. They talk about guys being restricted for going AWOL, and it is just confusing. They keep mentioning the fact, and I have just got it in my mind that I have been AWOL without knowing it. I remember when Abby, the fellow who takes the electrocardiograms. It seems that when they brought me down here in a wheel chair I thought . that they were going to shoot me or something. That is what I was thinking. It seems that I thought I had done something wrong in town. I thought that I had committed a sexual offense of some sort. I believe it was called rape at the time, and it still is. It seems as though I thought it was in front of some depot or station or something, and I thought there was a picture of it sent to my home town paper.

I thought one of the sergeants stood alongside of the car and took a picture of it, and the sergeant who was sleeping next to me was going to put it in the home town paper. So I thought that they were going to shoot me when I came down to your ward, Sir.

"When reading, I just can't seem to concentrate. It seems like some one just walks up to me. Physically I feel that I am pulsating in my body. I feel more or less a nerve pulsating in my back or something like that. I feel as though I have to urinate all the time. That's the feeling I have. The boys have been telling me about the x-rays and things that you have to get in order to get out of the ward. . . . swallowing some kind of paste and they take an x-ray of it. I suppose just to see if there is actually anything wrong inside. The nurses sometimes walk through and ask us if it is the rheumatic fever ward or the romantic fever ward.

"I guess I am just too serious. I sit around and listen to the other guys' sicknesses and troubles, what they say about blood pressures, etc., and I just wonder what I might have. My father seems to think there is some improvement. I called him long distance and told him I thought I could get over it."

The patient was discharged to the Veterans Administration Hospital near his home five months after his admission. He remained there for one month and was then discharged home.

This patient had acute rheumatic fever, with involvement of the aortic valve and the development of mild aortic insufficiency. The preceding scarlet fever is accepted as the first phase of the infection. Seventeen days later his rheumatic fever began with fever and severe headache. This is the initial complaint which can be ascribed to the central nervous system. The later findings of increased spinal fluid protein content and an abnormal colloidal gold curve corroborate the clinical findings of diffuse cerebral involvement.

The psychotic state in this case of rheumatic fever is interesting for the variety of symptomatology which is involved. There is the phase of acute delirium, with notable restlessness. He later showed definite depression, with self accusation, gave expression to feelings of guilt and was suicidal. He also at times showed the cataleptic-like phenomena. There were definite paranoid delusions of reference and persecution. At times he showed what suggested a severe psychasthenic-like state. The clinical picture before discharge from this hospital to a Veterans Administration Hospital was not unlike that of schizophrenia of the paranoid type, with some deterioration. Such a diagnosis would readily have been made if the history of the case were unknown. In addition to delusions, hallucinations played a prominent role even during the nondelirious phase of the illness. However, in the interview on the one hundred and eleventh day he showed remarkable ability to talk of his symptoms in such a manner as to indicate a relatively intact personality.

The social history obtained from interviews with the patient's father, brother and sister indicates a healthy normal personality structure. In the army he had made an excellent adjustment, and he had become an instructor in the radio school and was rated as superior. His motivation and attitude toward military service were even above the average. Prior to his illness he was considered to have had an excellent sense of humor and was described by his family as a "kindly, easygoing" person. He was neat about his appearance but not to any neurotic degree. He had never been arrested either in civilian or military life. He was brought up in a fairly strict home but was not subjected to any sadistic type of discipline. His correspondence with his family indicated that he "liked the army" and was adjusting well. Inquiries of his commanding officer cor-

tion was present in this patient during the period of mental changes. In addition, when salicylate was given later and the plasma level raised 10 mg. above that present at the onset of the delirium, hyperventilation appeared but no delirium. While this is not definite proof, it is suggestive evidence to support a diagnosis of cerebral rheumatism.

CASE 3.—A 27 year old white man was admitted to the hospital on June 6, 1945, with scarlet fever due to group A type 19 hemolytic streptococci. He had an uneventful course and was discharged on July 4, 1945. On cardiac examination the heart was normal. He was readmitted on July 9, complaining of malaise, generalized aching and a moderate cough. He had noticed that his heart was beating irregularly for four to five days. The family history was noncontributory. He had had rheumatic fever at the age of 7, but he did not remember any of the details of the illness.

Physical examination showed a tall, thin, blond man. The temperature was 100 F., the pulse rate 60 and the respiration 20. The heart was not enlarged and the rhythm was irregular, with dropped beats. There was a moderately loud aortic diastolic murmur. Electrocardiograms showed auriculoventricular dissociation. On the seventh day in the hospital the P-R interval was 0.36 seconds, and it did not reach a normal level until the sixtieth day in hospital. The sedimentation rate was 65 mm. per hour (Westergren) on admission, rose to 73 mm. per hour in the tenth day and returned to normal on the fifty-seventh day in the hospital. The antistreptolysin titer was 833 units per cubic centimeter. He was treated with small amounts of salicylate for symptomatic relief only. The aortic diastolic murmur persisted until his discharge from the hospital, and in addition a grade 2 apical systolic murmur appeared.

This man had completed an army radio course without difficulty. During his stay in the hospital with scarlet fever he had been a normal, well oriented soldier. It was noted on his admission to the hospital with rheumatic fever that he was extremely quiet and reticent and that he gave his history in a hesitant manner. He was oriented as to time and space, but his slow, hesitant manner and speech were noted by all who saw him. His face was expressionless. He had difficulty in sleeping for the first three weeks, but then he became more animated and began to take some interest in the other patients in the ward. His convalescence was slow. He quickly lost all his generalized aching after salicylate therapy, but when he was allowed up he complained of fatigue and vertigo. In an interview with the psychiatrist on the thirty-second day in the hospital he expressed concern over his inability to concentrate and remember things he had read. He had difficulty with simple subtraction. He complained of extreme tiredness and fatigue. Neurologic examination showed a gross tremor of the protruded tongue. There was a tendency to a masked facies. The gait was deviated to the left, with more swinging of the left arm while walking. The biceps reflex was more active on the right. Lumbar puncture on the one hundred and twenty-ninth day in the hospital showed no abnormalities. He slowly improved, and he was discharged from the hospital after one hundred and eighty-six days.

The possibility of rheumatic encephalitis was not recognized in this patient until in his convalescence. However, the change in his appearance and behavior from his admission to the hospital for scarlet fever and his admission for rheumatic fever was striking. His own account of his reactions and sensations during his illness and convalescence sug-

gests that he had a diffuse cerebral involvement. At the time of his discharge his actions and facial expressions were much more animated though still not considered normal.

CASE 4.—A 20 year old white youth was admitted to the hospital, complaining of a cough, chills and fever. His mother had had rheumatic cardiac disease. His past history was noncontributory. Examination showed only an acute infection of the upper respiratory tract. Ten days later, roentgenologic examination showed a moderate pleural·effusion on the right side. Culture of this fluid showed no growth. On the eighteenth day in the hospital a typical scralatiniform cutaneous eruption appeared, with an acute pharyngitis, and a diagnosis of scarlet fever was made. He was given sulfadiazine and scarlet fever convalescent serum. He was acutely ill for several days but then improved. On the forty-sixth day he was transferred back to the general medical service with the pleural effusion on the right side still present. This slowly absorbed, and the pleural cavity had cleared on roentgenologic examination on the ninety-seventh day in the hospital. On the fifty-ninth day he had an elevation of temperature to 101.4 F., and the pulse rate was 120. For the following five days he had hypochondriacal delusions and also complained that the other patients were talking about him. He was convinced he was going to die. He walked about the ward and refused to remain in bed. He had difficulty in sleeping and was hard to control at night. After several days he quieted down but still showed considerable concern over his condition. He had a foolish laugh and smile. Examination of the spinal fluid on the seventieth day showed no abnormalities.

On the sixty-fifth day he first complained of pain in the left foot and knee. The knee was swollen and showed a small effusion. There was a grade 1 apical systolic murmur where none was present before. The electrocardiogram on the sixty-ninth day was normal but showed a P-R interval of 0.24 three days later. Two weeks later the P-R interval was normal but changes had appeared in the T waves in leads III and IV. The sedimentation rate was 100 mm. per hour (Westergren) on the sixty-sixth day, and it remained elevated until the one hundredth day in the hospital. He was discharged after one hundred and twenty-eight days in the hospital, with a persistent grade 2 apical systolic murmur.

The patient's first manifestations of rheumatic fever were fever and sudden pronounced mental changes on his fifty-ninth day in the hospital. Several days later the acute symptoms in the joints appeared. Examination of the spinal fluid showed no abnormality to confirm the suspicion of cerebral involvement. However, it may be that in mild conditions this would not be expected or the changes may disappear quickly.

CASE 5.—A 26 year old white man was admitted to the hospital on Nov. 1, 1942, with an acute infection of the upper respiratory tract. He was discharged after four days. On November 21 he was readmitted, with severe pain in the arms and legs. Three days later a pericardial friction rub developed, with considerable pain in the chest and a temperature of 103 F. He was acutely ill. The white blood cell count was 28,300. Examination of the urine revealed it to be normal. Several cultures of the blood showed no growth. Electrocardiograms showed inversion of the T waves in all leads. He slowly recovered, and he was discharged after one hundred and sixty-five days in the hospital. He had no abnormal mental reaction, but on the thirteenth day a partial paralysis of the left

third nerve developed, with ptosis of the left lid and diplopia on looking upward and to the right. The paralysis cleared up quickly and after three days had disappeared.

This patient showed focal signs of cerebral involvement, with partial paralysis of the third nerve. There was no delirium. Subacute bacterial endocarditis was suspected, but cultures of the blood were repeatedly sterile, and no other embolic phenomena appeared.

<div align="center">COMMENT</div>

These cases represent our experience with cerebral manifestations in 207 patients with rheumatic fever observed over a three year period in an army post in the Midwest. From our experience and that of others, it is evident that acute cerebral reactions do occur during the course of rheumatic fever and may constitute a serious problem in treatment and prognosis. The mental symptoms may occur as the presenting picture and with little or no arthritic manifestations (case 1). They may precede the arthritic symptoms (case 4), or they may follow the arthritic symptoms and at a time when the patient seems well on the road to recovery (case 2). Usually the reaction indicates a diffuse involvement of the brain and there are minimal, if any, localizing signs. However, the patient in case 5 showed only a localized lesion. Anatomically, it was difficult to account for the findings on the basis of an embolus in this case, and we felt that there was a more diffuse lesion, with edema. There was complete clearing in several days, with no residual paralysis.

Rheumatic encephalitis may present a bizarre picture, with hallucinations, phobias and acute panic-like episodes. Delirium, restlessness and even convulsions may appear. In some cases a masklike facies, mental retardation and sleeplessness may be the only symptoms of cerebral involvement. Hyperpyrexia may be a serious complication. It did not occur in our patients, but it has been observed by others.[15] In some patients focal lesions, suggesting the peripheral embolic phenomena of bacterial endocarditis, may be the manifestation of cerebral involvement. In our first patient the spinal fluid showed no increase in cells but an increase in protein content. Our other patients showed no changes. Frisch's [11] patient showed a small increase in globulin content in the spinal fluid and an increase in the cells, with 80 per cent lymphocytes.

The use of large amounts of salicylate in the treatment of rheumatic fever may cause difficulty in establishing a diagnosis of rheumatic encephalitis because of the possibility of salicylate toxicity. Severe salicylate toxicity, with delirium, is usually preceded by a peculiar type

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15. Swift, H. F.: Rheumatic Fever, in Cecil, R. L.: Textbook of Medicine. ed. 5, Philadelphia, W. B. Saunders Company, 1941.

of hyperventilation.[16] This respiratory picture is present and increased in severity in the phase of delirium. Hyperventilation was not present in our cases of rheumatic encephalitis. When it is present, the discontinuance of the use of salicylate and the administration of sodium bicarbonate will serve to relieve the respiratory difficulty and the delirium if due to excess salicylate. The importance of recognizing this hyperventilation in the prevention of severe salicylism has been emphasized.[16]

In our experience, the use of sodium salicylate is of no benefit in the treatment of rheumatic encephalitis. Others have found this true in chorea.[15] In our second case the patient had what may have been encephalitis while receiving large doses of salicylate. Encephalitis developed in Dobbs and de Saram's [12] patient while he was receiving sodium salicylate, and in Frisch's [11] case symptoms developed four days after the use of salicylate was stopped. Dobbs and de Saram [12] used an anesthetic agent, solution of tribromoethanol, to control the maniacal delirium. Such measures may have been indicated in our first case and certainly should be considered in wildly maniacal states to prevent physical exhaustion and additional cardiac damage.

CONCLUSIONS

The pathologic changes and symptoms of rheumatic encephalitis are reviewed. One case of rheumatic encephalitis is reported in which there were decided mental changes, with apparent recovery. Four other cases are presented in which cerebral involvement due to acute rheumatic fever seemed probable.

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16. Warren, H. A.; Higley, C. S., and Coombs, F. S.: The Effect of Salicylate on Acute Rheumatic Fever, Am. Heart J., to be published.

TEST FOR QUANTITATIVE VIBRATORY SENSATION IN DIABETES, PERNICIOUS ANEMIA AND TABES DORSALIS

Diagnostic and Prognostic Value

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THERE are a number of systemic diseases, largely dealt with by workers in internal medicine, in which neurologic complications play a highly important role and in which a correct evaluation of signs and symptoms is of utmost importance in diagnosis and prognosis.

The neurologic changes which are considered here are those involving the peripheral nerves, the posterior nerve roots and the spinal cord as they appear in patients with diabetes mellitus, pernicious anemia and tabes dorsalis. Of the many and varied neurologic signs and symptoms presented by such patients, the major interest in this discussion is loss of vibratory sensation.

Diminution or loss of vibratory sensation also occurs in diseases other than diabetes. Various observers have noted this in patients having lesions in the cord and in cases of multiple peripheral neuritis, especially those involving lead poisoning and poisoning due to alcohol. It has also been noted in transverse myelitis, in the spinal form of hereditary sclerosis, in syphilitic meningomyelitis and in disseminated sclerosis.

Pathologic studies in many but not in all cases in which vibratory sensation was most altered have revealed well defined lesions within the cord as well as in the peripheral nerves, thus establishing the concept of this manifestation of disease on a relatively sound clinical basis.

While it is true that altered vibratory sensitivity may not be discovered in diabetes, pernicious anemia or tabes dorsalis before the disease has made certain inroads on the patient, it is equally true that this altered vibratory sense may be one of the early clinical manifestations of disease.

Aside from its value in diagnosis and prognosis, the existence of an impaired vibratory sense is forceful evidence of the need for intensive or effective treatment. This has been abundantly proved in cases of diabetes mellitus and pernicious anemia. In tabes dorsalis, the need for treatment and its intensity should be tempered with clinical judgment and skill.

METHOD

The significance of vibratory sense has been appreciated for many years. Beginning with Rumpf [1] in 1889, many observers have applied this method of study to physiologic and pathologic states. Various methods for the elicitation of the vibratory sense have also been suggested. Early in these studies, tuning forks of different vibratory rates, from 13 to 1,000 vibrations per second, were used.
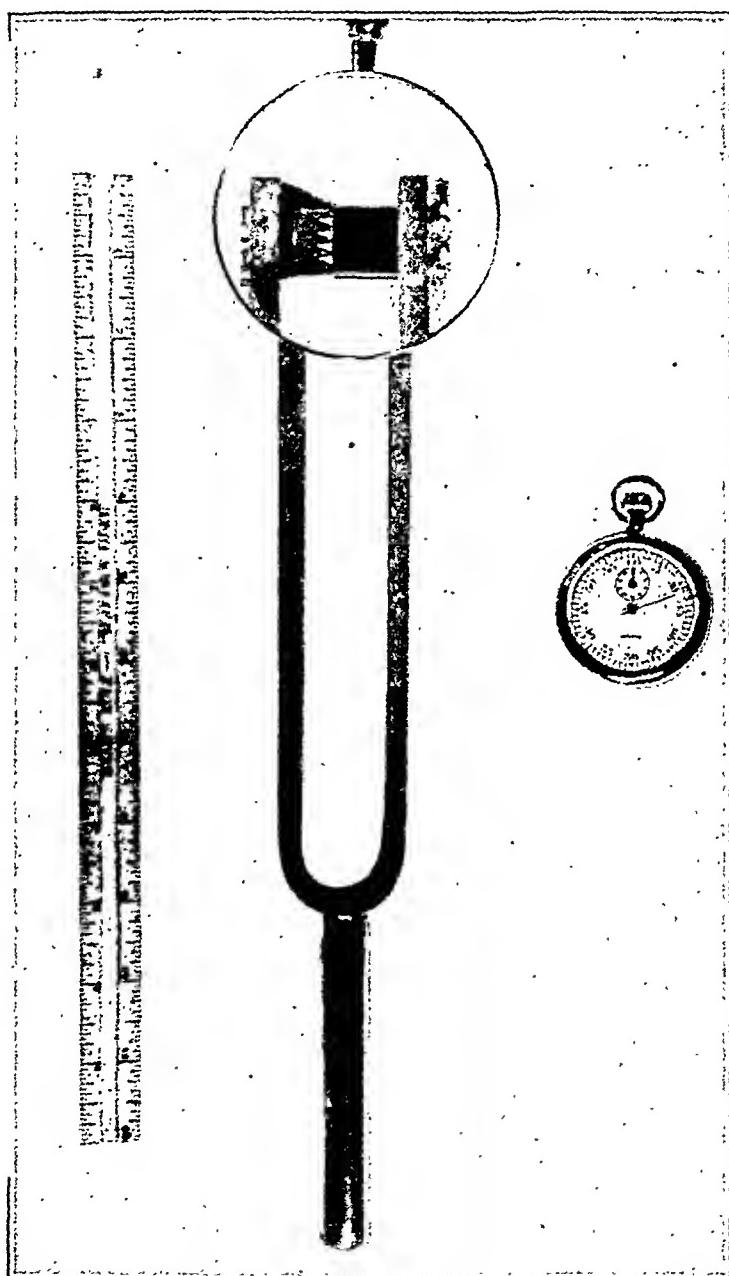
Fig. 1.—The Symns tuning fork, used in the study of vibratory sensation.

1. Rumpf, A.: Ueber einen Fall von Syringomyelie nebst Beiträgen zur Untersuchung der Sensibilität, Neurol. Centralbl. **8**:185 (April 1); 222 (April 15) 1889.

Gray [2] in 1932 used a tuning fork with a rate of 120 double vibrations per second. By placing a coil between the prongs of the tuning fork and energizing this coil with an alternating current, the vibratory rate of the fork could be accurately controlled.

A simpler method, and one that has been used by my colleagues and me since 1922, is the 13 inch (33 cm.) tuning fork adopted in 1911 by Symns,[3] of Guy's Hospital, London, England. It is a comparatively large and heavy fork with a long handle, responding with 108.75 double vibrations per second. The fork is struck, and when a correct amplitude is attained the handle of the fork is quickly applied to certain bony prominences of the body. The duration of vibratory perception at each of these areas is measured with a stop watch, and the number of seconds is recorded. Normal values have been established by Symns,[3] Wood[4] and others. This method is entirely practical, and it is· sufficiently accurate for clinical purposes. Its simplicity enhances its reliability and usefulness.

Figure 2, a modification of the chart by Wood, is based on the accepted normal values; it is the one that we use in recording our observations. The elective points
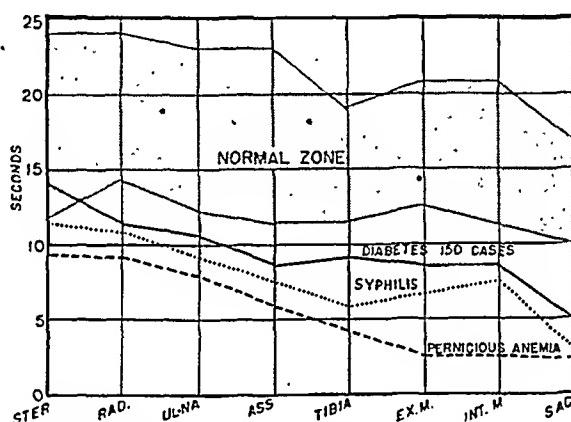
Fig. 2.—At these areas—sternum, radius, ulna, anterior superior spine, tibia, external malleolus, internal malleolus and sacrum—readings were made with the Symns tuning fork, which is 13 inches long, with 112 double vibrations per second. The graph represents average values for 135 diabetic patients, and this curve is definitely below the normal.

for the estimation of the vibratory sense are the sternum, radius, ulna, anterior superior spine of the ilium, tibia, external malleolus, internal malleolus and sacrum. I have changed the arrangement of the original chart so that the curve presented here corresponds to the anatomic levels of the spinal cord.

It will be noted, first of all, that the sensitivity of the upper half of the body is greater than that of the lower half. This is true both in health and in disease. In diabetes, in pernicious anemia and in locomotor ataxia, the neurologic signs and symptoms are more pronounced in the lower half of the body. If improvement does occur, the upper half of the body will show this improvement earlier

2. Gray, R. C.: A Quantitative Study of Vibration Sense in Normal and Pernicious Anemia Cases, Minnesota Med. **15**:674 (Oct.) 1932.

3. Symns, J. L. M.: An Accurate Method of Estimating the Vibratory Sense, Brit. M. J. **1**:539, 1912.

4. Wood, E. J.: A Further Study of the Quantitative Variations in the Vibration Sensation, Am. J. M. Sc. **163**:19 (Jan.) 1922.

and to a greater degree than the lower half. In the normal person, while at the sternum the perception is of an average duration of twelve to twenty-four seconds at the sacrum it is of an average duration of ten to seventeen seconds. The tuning fork vibrates at all times at a fixed rate; its vibratory rate is unalterable.

· PHYSIOLOGY

For a correct interpretation of the findings in this procedure, it should be recognized that soft tissues, particularly the skin and its tactile sense, play a minor role in transmission of vibratory sensation. It seems that tactile sensation and vibratory sensation are factors apart.

Vibratory sensation is induced by placing the vibrating tuning fork on one of the bony prominences of the body, from which the vibratory sense is transmitted along sensory paths leading to the cord and brain. In this, bone conduction plays an important role. Vibratory sensation is thus transmitted from its point of origin to the posterior roots, then to the posterior column and then upward. Vibratory sensation, as a whole, depends on the patient's sense of touch, the pressure sense and the degree of sensation transmitted by muscles, bones and joints.

There are a number of factors entering into the interpretation of the values obtained which must be recognized: 1. Vibratory sensation varies in different persons. Some are more sensitive while others are less sensitive to vibration. 2. Vibratory sensation tends to diminish with the advance of years. It is lower after middle life. 3. It has been noted by Gray [2] that for some unexplainable reason the left side is more sensitive to vibration than the right side of the body, except over the anterior surface of the tibia, the malleolus and the fibula. We have verified the correctness of this observation. 4. Edema of the soft tissues interferes with perception of the vibratory sense. 5. Paresthesias as they occur in sensory neuritis may tend to confuse the results of the examination for vibratory sensation.

PATHOLOGY OF DIABETES MELLITUS

In diabetes mellitus, neurologic complications, as they are seen from day to day, are so common that a reported incidence of 50 per cent [5] does not seem high enough. If the patients lived longer, no doubt the incidence would reach a higher figure. Apparently no part of the nervous system is immune to involvement. With varying frequency, the peripheral nerves, the roots, the spinal cord and the brain show evidences of pathologic change. In this disease, the distribution of lesions in the cord and peripheral nerves makes it apparent that periph-

5. Jordan, W. R.; Randall, L. O., and Bloor, W. R.: Neuropathy in Diabetes Mellitus, Arch. Int. Med. **55**:26 (Jan.) 1935. Jordan, W. R.: Neuritic Manifestations in Diabetes Mellitus, ibid. **57**:307 (Feb.) 1936. Jordan, W. R., and Randall, L. O.: Neuropathy in Diabetes, ibid. **57**:414 (Feb.) 1936.

eral involvement is not secondary to the proximal lesions in the spinal roots or the cord. Isolated lesions are found both in the cord and in the nerves, and they are independent of each other. In diabetes the peripheral nerves are more frequently involved and show greater change than the more central structures of the cerebrospinal nervous system. This is in striking contrast to the findings in pernicious anemia, in which the peripheral nerves suffer less and the central nervous system suffers more.

The pathologic lesion commonly seen is parenchymatous neuritis. It may be degenerative or inflammatory. Degeneration is seen in the myelin substance and in the axis-cylinder.[5] Where the changes in the nerves are found to be most striking, there the accompanying vascular change and arteriosclerosis are also most striking. Changes in nerves and blood vessels go together. These concurrent findings explain the coincidental clinical symptoms in the diabetic patient.

Jordan[5] and others have investigated the chemical changes in the diseased tissue of the nerve in such cases, with the following tentative conclusions:

Chemical analysis shows an increase in water and protein content. The cholesterol may be increased or diminished; the total lipids are generally increased; in some they are lower than normal. More so the phosphatids show an increase. There is an increase in the water-soluble phosphorus compounds. The more severe clinical cases showed greater change in the lipid fraction. On the whole, while the chemical studies up to the present time are interesting indeed, it may not yet be said that they are conclusive; there is more to be learned here. Correlation of clinical and pathologic studies has as yet failed to show an immediate or direct relationship between glycosuria, hyperglycemia, the ketosis of diabetes and the neurologic complications of the disease. The process is a degenerative one and therefore a slower one.

PATHOLOGY OF PERNICIOUS ANEMIA

Goldhamer and his associates,[6] in a study of 461 cases of pernicious anemia, found clinical evidences suggesting changes in the spinal cord in 89.2 per cent of the entire series. Of the 461 patients, 53 died. Of the 53 that died, 17 had been confined to bed because of progressive changes in the cord. Ten out of 11 cases came to autopsy, and in them widespread combined degeneration of the cord was a constant finding. As to the existence of true peripheral neuritis in pernicious anemia, Goldhamer said, "neuropathologists are not in agreement on this point."

6. Goldhamer, S. M.; Bethell, F. H.; Isaacs, R., and Sturgis, C. C.: The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia, J. A. M. A. **103**:1663 (Dec. 1) 1934.

In pernicious anemia loss of vibratory sense occurs early in the disease, while symptoms suggesting peripheral neuritis are vague and indefinite. Thus it appears that the sensory manifestations in this disease are primarily those of involvement of the cord rather than disease of the peripheral nerves. Cabot (cited by Needles) many years ago found involvement of the cord in 84 per cent of patients with pernicious anemia. Clinical observations in patients over long periods clearly show that certain persons have a positive tendency toward involvement of the nerves while others are relatively immune to neuropathologic changes.

SYMPTOMS, DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A helpful and inclusive outline for the recording of clinical findings in these cases is that suggested by Goldhamer.[6] Any of these symptoms may be found in patients belonging to the groups under discussion.

A study of the vibratory sensation is of value in the differential diagnosis in cases of tabes dorsalis. It is useful in the differentiation of gastric crises or girdle pains from other forms of abdominal pains presenting a more or less obscure symptomatology. Vibratory sensation is already altered at the time these pains first appear, as shown in the cases to be cited later.

The lowest readings are ordinarily obtained at the sacrum. Our own experience does not warrant the interpretation of the "sacral dip" as being characteristic of any one disease. It is the curve as a whole which is significant and the significance of the curve lies in its relation to the normal level, as it is found in health.

CLINICAL OBSERVATIONS

With the technic described we have made numerous observations on the vibratory sensation in cases of diabetes mellitus, pernicious anemia and syphilis of the central nervous system. For a period of twenty years we have found it helpful in evaluating the patient's condition and the progress of the disease. We are still repeating the test at intervals in patients whose first examinations were made at the beginning of our studies fifteen years prior to the writing of this paper. In one sense the curve serves as an index of the patient's condition, inasmuch as it reflects deterioration or improvement. Here it must also be assumed that not only has the patient whose curve has not fallen noticeably in ten to fifteen years withstood the disease but he has also not suffered too much from the physiologic downward course, which to a certain extent is to be expected. That in itself is a gain. Some patients under effective treatment show a positive gain, as the charts show; in only a few of our observations has there been a decided discrepancy between the level of the vibratory sensation curve and the clinical course of the disease.

Evaluating the Curve.—Since quantitative values are being dealt with here, measured in seconds' duration of the vibratory sensations, it is somewhat clarifying to place this measurement on a quantitative basis. This is done in the following way: The zone for perception of vibratory sensation exists within a range of low and high normal values. As figure 3 shows, the duration of vibratory sense over the sternum is normally not more than twenty-four seconds and not less than twelve seconds. If the values in the upper curve are totaled by adding the number of seconds, the sum of one hundred and seventy-two seconds is obtained. If the values of the lower curve are totaled, a total of ninety-three seconds is obtained.

By this method of calculation, it is found that in a case of pernicious anemia in the first year there was a total of fifty-three seconds, in the second year a total of thirty-six seconds and in the sixth year a total of twenty-seven seconds. All these are far below the normal curve, which has a minimal total value of ninety-three seconds. This gives an index of 27/93 for this patient at the last examination. For a patient with tabes dorsalis there was an index of 12/93.

Evaluating the Progress of the Disease.—Some of the accompanying charts show that when our therapeutic efforts were successful there was also an improvement in the vibration curve. This was most striking in cases of pernicious anemia and in diabetes. Certain cases of tabes dorsalis likewise indicated arrest of the downward course of the disease.

Clinical Observations in Diabetes.—There are diabetic patients in this group of 150 cases who have been under our care for fifteen years, and curves at varying intervals reveal their vibratory sensation during that period. Of these, some have shown definite improvement under treatment, others have shown comparatively little change while still others have suffered a definite deterioration with advance of the disease. The striking observation was to see the curve approach the normal or recede away from the normal with improvement or aggravation of the diabetic state. The average level for the entire series is distinctly below the normal level. It was further noted that the type of curve, e. g., the points at which sensation was lower in certain persons, was found to be the same at each successive examination, so that a certain type of curve becomes characteristic for the patient, thus indicating the actual site of maximum physiologic or pathologic change. The vibration curve may be as characteristic for the patient within certain limitations as his retinal vessels or his fingerprints.

Quantitative Change.—Since change in the curve is based on quantitative measurements in seconds, the total value of the curve may be evaluated in terms of seconds' duration. On that basis, as already stated, the upper curve of vibratory sensation has a total value of one hundred

and seventy-two seconds, while the lower curve has a total value of ninety-three seconds. If the entire series of 150 diabetic patients is taken; it is found that the average value for the curve in this disease is sixty-eight and one-half seconds, definitely below the normal zone. A survey of the entire group likewise shows a parallelism between the youth of the patient, the mildness or severity of the diabetic state and the physical deterioration and senility of the patient. Altogether, a definite relationship is found between damage to the patient and the level of vibratory sensation.

The accompanying charts indicate the level of vibratory sensation and increase or decrease of sensation with improvement or deterioration in the patient's condition. The following are summaries of some of the cases.

CASE 1.—A girl, aged 10 when first seen for diabetes, has grown normally and is in apparent good health. She now takes 18 units of crystalline insulin twice daily. The last curve in her chart actually reflects her improved state.

CASE 2.—A boy aged 10 was brought to our notice in 1932. Four years later he was in good health. He now takes 60 units of insulin daily, is growing normally and is in a good nutritional state. During the past four years improvement has taken place.

CASE 3.—A man whose present age is 55 has been under observation for fourteen years, and his condition is still within the normal zone. There has been no evidence of deterioration over fourteen years. His condition is well controlled, 10 units of insulin daily being taken. His nervous system withstands the effects of the disease.

CASE 4.—A woman aged 58 has diabetes of twelve years' duration. Coincidental with the diabetes, this patient has pernicious anemia. It will be noted in her chart that beginning at the cord level indicated at the anterior superior spine of the ilium there has been a complete loss of vibratory sense during the past two years. There is no vibratory sensation in the lower half of the body, suggesting tabes diabetica.

CASE 8.—The patient first came under our care in 1922, at the age of 50. He has a severe form of diabetes, requiring 40 units of insulin daily. From 1922 to 1932 there was considerable physical deterioration. During that period he lived on a high fat diet. When he consulted us again in 1932, he was placed on a low fat, high carbohydrate diet and has shown much improvement since then. The 1936 curve on his chart also indicates this improvement. Whether an excess fat and low vegetable diet was responsible for the deterioration and whether a better diet, with all that a good diet implies, accounts for the improvement cannot be stated at this time.

CASE 9.—A woman aged 71 had tabes diabetica, with vascular degeneration. She died of cerebral hemorrhage six months after the time of the last curve on her chart. There was decided degeneration in three years.

CASE 10.—The patient was a man aged 51 who took 32 units of insulin daily. There was slight deterioration after ten years. His general condition is good after fourteen years of treatment with insulin.

In cases 10 and 3 the diabetes is of twenty-one and seventeen years' duration respectively. Both patients are superintendents in mills and are physically and mentally active. It is possible that their healthful
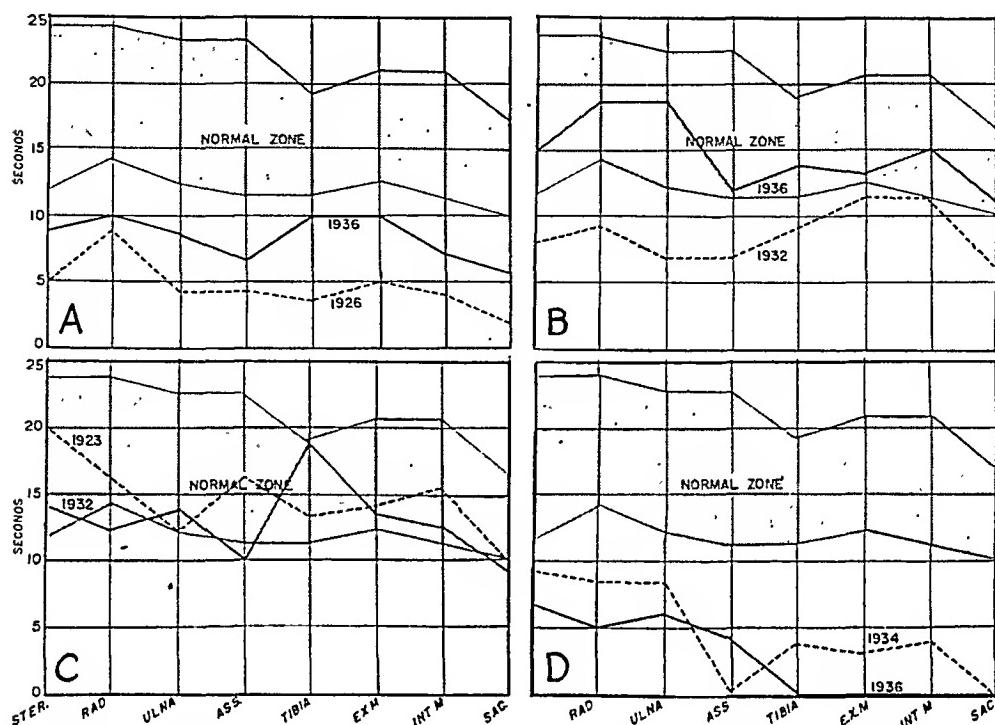
Fig. 3.—Vibratory sensation. *A*, case 1. *B*, case 2. *C*, case 3. *D*, case 4.
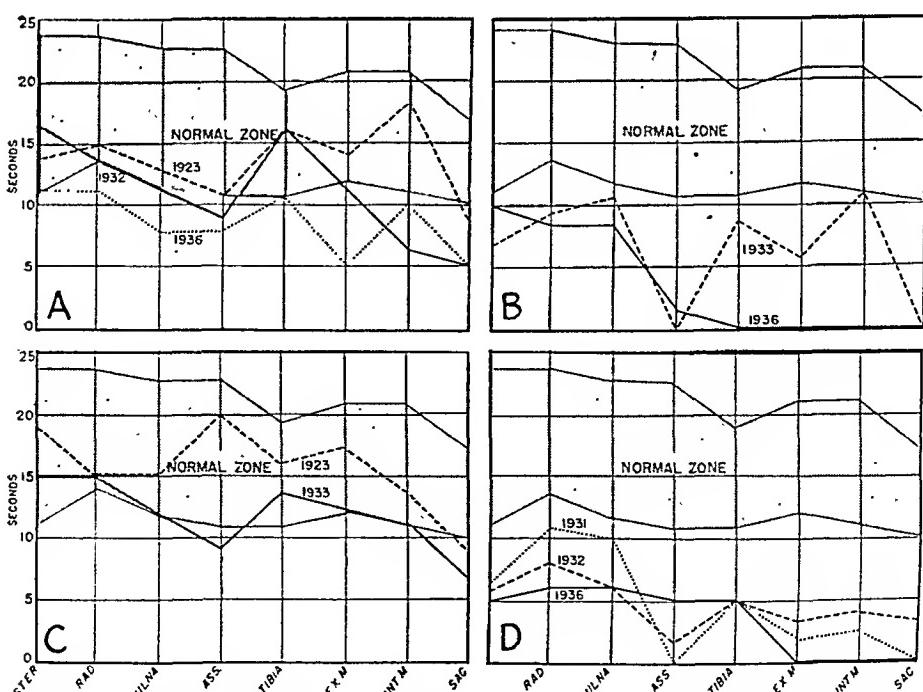
Fig. 4.—Vibratory sensation. *A*, case 5. *B*, case 6. *C*, case 7. *D*, case 8.

occupations are more conducive to better nutrition and function than are the occupations of many of our other patients who live sedentary lives. It may also be that, aside from the factor of youth, a more healthful mode of living accounts for the better curves found in the charts of younger patients and of children.
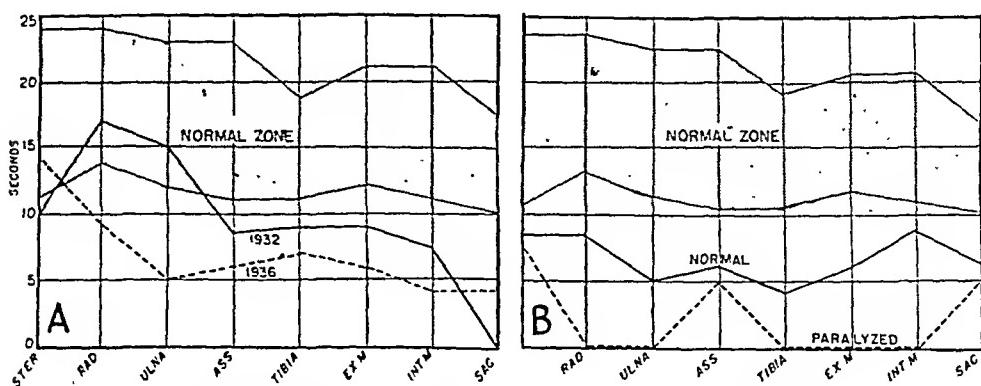
Fig. 5.—Vibratory sensation. *A*, case 1. *B*, case 2.

Quantitative Loss in Vibratory Sensation.—The accompanying table indicates the extent of loss in a group of diabetic patients and the gain in another group in the course of two to seventeen years.

Vibratory Sensation in Patients with Diabetes

	Loss				Gain		
Case	First Reading, Seconds	Period After Which Reading Was Made, Yr.	Loss, %	Case	First Reading, Seconds	Period After Which Reading Was Made, Yr.	Gain, %
A............	146	9	50	H...........	69	2	50
B............	60	3	50	I...........	65	2	33
C	125	10	25	J...........	80	14	14
D............	65	4	24	K...........	56	4	6
E............	81	7	10	L............	71	4	5
F............	78	2	10				
G............	118	9	8				

PERNICIOUS ANEMIA

In pernicious anemia loss of vibratory sensation is an early symptom and a striking one. The tuning fork has proved to be a useful instrument in the study of this disease; it offers a clue as to diagnosis, and it may serve as well as an index to prognosis and treatment. The patient with pernicious anemia complains first of disturbed sensation in the upper extremities; pains, paresthesias and anesthesias follow, and with these comes diminution or loss of vibratory sensation. In contrast to this, the diabetic patient complains first of symptoms referable to the lower extremities, the legs and the feet. The other striking

contrast is in the fact that while in pernicious anemia it is the cord that is affected more in diabetes it is the peripheral nerves.

In pernicious anemia, as in diabetes, each case presents individual points of clinical interest which are reflected in the vibratory sensation curves and complement the clinical picture of the disease. The tendency of the curves in this disease is downward unless effective treatment is applied early. One of the most striking cases in which the patient showed improvement under liver therapy was that of a woman, aged 55, who arrived at the hospital walking with difficulty on two crutches. Intensive treatment was instituted, the patient was up and about within two months and at the end of six months she was again driving a large limousine, with apparent complete control over arms and legs. Neurologic improvement can and does occur with successful therapy.

A complete study of this disease is that of Hyland and Farquarson,[7] whose experience in 74 cases has convinced them that improvement is attained when treatment is early and thorough and that rigorous treatment applied early in the disease will prevent degeneration of the cord. They consider impairment of vibratory sensation of diagnostic value in pernicious anemia even before the blood picture is fully developed.

TABES DORSALIS

In this disease the vibratory sensation is strikingly lower than normal, varying with the degree of damage at the time of examination. It has been said that the sacral dip is characteristic of this disease, but that is obviously incorrect. The sacrum represents the lowest portion of the spinal cord. In fact, zero readings are found just as frequently in diabetes and pernicious anemia as they are in tabes dorsalis. Our readings in these cases over a period of years show that the curve improves with therapeutic control of the disease. The vibratory sensation curve is of distinct value in the differential diagnosis of gastric crises, as repeated experience has shown.

SUMMARY AND CONCLUSION

A study of the vibratory sensation as estimated with the tuning fork is a clinical method of diagnostic and prognostic value. Vibratory sensation is largely independent of tactile sensation, and it depends on the transmission of vibratory sense through muscle, bone and joints to the peripheral nerves, posterior roots and posterior columns of the spinal cord to the brain.

A normal curve, based on the number of seconds' duration of the vibratory sense as induced by a vibrating tuning fork, has been estab-

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7. Hyland, H. H., and Farquarson, R. F.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, Arch. Neurol. & Psychiat. **36**:1166 (Dec.) 1936.

lished. In certain diseases, notably diabetes mellitus, pernicious anemia and tabes dorsalis, the loss of vibratory sensation is so decided that the curve found in these cases is of diagnostic and prognostic value. Not only is this curve of confirmatory diagnostic value as to the existence of these diseases, but the rise or fall of the curve occurs simultaneously with improvement or aggravation of the disease, thus becoming of prognostic value. Notable deviations below the normal throw additional light on the need for intensive treatment of the disease. The level of the vibratory sensation rises as the patient's condition improves with successful treatment. It rises more in younger patients, whose recuperative power is greater. This is illustrated in our studies of diabetes, pernicious anemia and tabes dorsalis.

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TRANSITORY DIABETIC SYNDROME ASSOCIATED WITH MENINGOCOCCIC MENINGITIS

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THE PURPOSE of this paper is to emphasize the significance and frequency of a transient diabetic syndrome due to and occurring during incipient meningococcic meningitis. This condition was noted among the miscellaneous meningitides as early as 1884.[1] These early observations referred to cases of tuberculous meningitis.

The occurrence of glycosuria in meningococcic meningitis has been reported by Box and Nicholson,[2] Bruce and Flexner,[3] Ward and Driver,[4] Hunter,[5] McNally,[6] Cole[7] and Ferguson and Barr[8] (table 1).

Observations at South View Isolation Hospital during the last three years have indicated that this syndrome exists in a high proportion of cases of meningococcic meningitis. Findings of sugar and acetone in the urine and treatment of diabetic acidosis impeded the diagnosis of meningococcic meningitis in some instances. When these findings interfere with the final diagnosis of meningococcic meningitis a serious

1. Loeb, M.: Ein Erklärungsversuch der verschiedenartigen Temperaturverhältnisse bei der tuberculösen Basilarmeningitis, Deutsches Arch. f. klin. Med. **34**:443, 1883-1884.

2. Box., C. R., and Nicholson, T. G.: The Glycosuria Associated with Meningitis, Lancet **1**:239, 1917.

3. Bruce, J. W., and Flexner, M.: Meningococcus Meningitis: Report of an Unusual Case, Arch. Pediat. **43**:473 (July) 1926.

4. Ward, C. W., and Driver, A. A.: Meningococcal Meningitis Starting as Diabetic Coma, Lancet **2**:228 (Aug. 24) 1940.

5. Hunter, R. R.: Glycosuria in Meningococcal Meningitis, Lancet **2**:604 (Nov. 9) 1940.

6. McNally, W. D.: Meningitis with a Diabetic Coma, Illinois M.J. **80**:507 (Dec.) 1941.

7. Cole, L.: Diagnosis of Coma in Cerebrospinal Fever with Diabetes, Lancet **2**:421 (Oct. 10) 1942.

8. Ferguson, F., and Barr, D.: Glycosuria in Meningitis, Ann. Int. Med. **21**:173 (Aug.) 1944.

prognosis results. This paper will not involve itself in the diagnostic symptoms or in the treatment of this disease, as these have been covered in a previous article.[9]

ILLUSTRATIVE CLINICAL CASES

CASE 1.—M. N., a 65 year old white woman, was admitted to a general hospital on March 6, 1943 in a restless and disoriented state. The commitment papers gave a history of vomiting and anorexia of two weeks' duration.

On physical examination there was evidence of decided dehydration. The rectal temperature was 103.6 F., the pulse rate 92 per minute, the respiratory rate 26 per minute and the systolic blood pressure 166 mm. of mercury and the diastolic 80 mm. Internal strabismus of the left eye and rigidity of the neck were noted. No pathologic reflexes were observed. The urine contained sugar (3 plus) and acetone (2 plus). The blood sugar content was 168 mg. per hundred cubic centimeters.

TABLE 1.—*Instances of Glycosuria in Meningococcic Meningitis*

Authors	Total No. of Cases	Patients Previously Diabetic	Cases of Post-infusional Glycosuria	Cases of Meningococcic Glycosuria		
				Total No.	Patients with Diabetes After Meningitis	Patients Treated for Diabetic Acidosis
Box and Nicholson........	3	?	0	3	All fatal	Not reported
Bruce and Flexner........	1	?	0	1	0	1
Ward and Driver..........	1	0	0	1	0	1
Hunter...................	1	0	0	1	0	1
McNally..................	1	0	0	1	Not reported	1
Cole.....................	4	2	0	2	0	2
Ferguson and Barr........	12	1	2	9	0	2
Fox, Kuzma and Washam	58	0	2	56	0	5

From the findings a diagnosis was made of impending diabetic coma and cerebral arteriosclerosis with psychosis. Treatment with insulin, dextrose and fluids was initiated.

Fourteen hours after admission a lumbar puncture was performed, which yielded a cloudy fluid under normal pressure. A white cell count of 10,700 per cubic millimeter, with a predominance of polymorphonuclear leukocytes, was demonstrated. A smear from the centrifuged sample showed gram-negative diplococci which could not be morphologically identified with certainty as meningococci. A tentative diagnosis of pyogenic meningitis was made and parenteral and oral administration of sulfadiazine initiated. Treatment of the diabetes continued through the second day in the hospital. Opisthotonos, had developed by this time. The Kernig and Brudzinski signs were present, and fading petechiae were noted. A diagnosis of meningococcic meningitis was confirmed by a second examination of cerebrospinal fluid and the report of a twenty-four hour culture of the blood. The patient was transferred to South View Isolation Hospital on March 9, 1943, where sulfadiazine therapy was continued. She made an uneventful recovery. At the time of discharge urinalysis gave normal results.

9. Fox, M. J.: Penicillin in the Treatment of Meningitis, Wisconsin M. J. 44:1161 (Dec.) 1945.

CASE 2.—S. K., a 44 year old waitress, was brought to a general hospital on May 20, 1944, complaining of a stiff neck and frontal headache. A history was obtained of staggering and falling followed by convulsive movements. Preliminary examination revealed the presence of pronounced dehydration, petechiae over the arms and trunk and an odor of acetone on the breath. The Kernig and Brudzinski signs were present. The temperature was 102.8 F., the pulse rate 118 per minute, the respiratory rate 22 per minute and the systolic blood pressure 140 mm. of mercury and the diastolic 70. The urine contained sugar (4 plus) and no albumin. The blood sugar content was 179 mg. per hundred cubic centimeters. The spinal fluid was grossly cloudy, xanthochromic and under a pressure of 27 millimeters of mercury. The spinal fluid sugar content was too low to be determined. There were 9,300 white cells in the spinal fluid, of which 88 per cent were polymorphonuclear. Confirmation of the clinical diagnosis of meningococcic meningitis was made by demonstration of the gram-negative intracellular and extracellular diplococci on smear. Treatment with fluids, insulin, dextrose and sulfadiazine was instituted. The patient was transferred to South View Isolation Hospital and treated with parenteral administration of fluids and sulfadiazine. The convalescent course was uneventful, and the patient was discharged on the fourteenth day with sugar-free urine and without other evidence of diabetes mellitus.

CASE 3.—E. H., a 39 year old white man, was taken to a general hospital on July 4, 1943 in an extremely lethargic condition. A history was obtained of numbness and pain in his legs, severe throbbing headache and nausea. On examination there was pronounced rigidity. The pupils reacted sluggishly; other reflexes were hypoactive. The pulse rate was 100 per minute, with an irregular rhythm, and the systolic blood pressure was 140 mm. of mercury and the diastolic 80. Urinalysis on admission showed reaction which was positive for sugar (4 plus) but negative for acetone. The blood sugar content was 245 mg. per hundred cubic centimeters. The cloudy cerebrospinal fluid which was obtained on lumbar puncture contained 5,600 white cells per cubic millimeter, with a predominance of polymorphonuclear leukocytes. Gram-negative diplococci were identified as meningococci by smear and culture. Treatment consisted of administration of fluids, insulin, dextrose and sulfadiazine. The patient was transferred to South View Isolation Hospital and treated on an intensive sulfadiazine regimen. An uneventful convalescence resulted, and the patient was discharged without any evidence of diabetes mellitus.

CASE 4.—H. M., a 56 year old white woman, entered a general hospital on Sept. 26, 1943 in a semicomatose condition. The patient's family reported that she had become ill two days before admission with nausea, vomiting, generalized aches throughout the body and abdominal pain, her condition rapidly progressing to a stuporous state.

Examination on entrance revealed a temperature of 102.2 F., a pulse rate of 104 and a respiratory rate of 24. Urinalysis revealed a reaction which was strongly positive for albumin and sugar, but tests for acetone elicited a negative reaction. The blood sugar content was 283 mg. per hundred cubic centimeters. Treatment for diabetic coma was begun with solution of sodium r-lactate one-sixth molar, dextrose and insulin. Administration of sulfadiazine was added to the initial therapy about nine hours after admission. A lumbar puncture was performed about twenty hours after admission, yielding cloudy yellow cerebrospinal fluid under increased pressure containing 22,150 white blood cells per cubic millimeter which were predominantly polymorphonuclear. The presence of many gram-negative intracellular and extracellular diplococci which resembled meningo-

cocci was noted in the smear. The patient was transferred to South View Isolation Hospital, where, despite intensive sulfadiazine therapy, she became progressively worse and died during the first day in the hospital. The urine on that day contained sugar (4 plus) but no acetone.

CASE 5.—G. L., a 38 year old white woman, was brought to a general hospital on Dec. 20, 1945 in a comatose condition. A history from the relatives revealed that during the previous evening she had become ill with a headache, sore throat, stiff neck and chills, later becoming irritable and irrational. Physical examination on admission revealed numerous small ecchymoses on the skin, the Kernig sign, hyperactive tendon reflexes and an odor of acetone on the breath. The temperature was 102 F., the respirations were deep and rapid at a rate of 28 per minute, the pulse rate was 88 and the systolic blood pressure 110 mm. of mercury and the diastolic 70. Urinalysis revealed sugar (2 plus) and acetone (4 plus). Treatment for diabetic coma with large doses of insulin, parenteral sodium r-lactate one-sixth molar and physiologic solution of sodium chloride was instituted. Later, when the patient regained consciousness, the urine was essentially negative for sugar and acetone, and the blood sugar content was 100 mg. per hundred cubic centimeters. A lumbar puncture performed twenty-four hours after her admission to the hospital yielded a cloudy cerebrospinal fluid containing 4,000 white cells per cubic millimeter, of which 99 per cent were polymorphonuclear. Meningococcic meningitis was diagnosed. The patient was transferred to South View Isolation Hospital, where intensive sulfadiazine and penicillin therapy was instituted and use of insulin discontinued. Convalescence was uneventful, and the patient was discharged on the eleventh day with sugar-free urine and without symptoms of diabetes mellitus.

DATA FROM AUTOPSIES

In the city of Milwaukee there were 214 cases of meningococcic meningitis with 46 deaths in the past three years, distributed as follows:

Year	Cases	Deaths
1943	55	15
1944	105	18
1945	54	13
	214	46

During these years Dr. Joseph Kuzma and Dr. Myron Schuster, of Milwaukee County Hospital Pathology Department, performed seventeen autopsies at South View Isolation Hospital on patients with meningococcic meningitis, with the finding of a Waterhouse-Friderichsen syndrome in ten of the autopsies.

The pertinent pathologic observations in the seventeen autopsies on patients with meningococcic meningitis are as follows:

Gross pathologic changes are usually limited to the brain, wherein a prominent basilar accumulation of exudate is generally seen. This may be so striking as to obscure the cranial nerves and basilar vessels. The inferior surface of the cerebellum frequently exhibits a deep imprint of the foramen magnum, producing distinct cerebellar tags surrounding the medulla. The exudate on the convexities of the brain is variable in amount. The brain substance itself usually exhibits perivascular

edema and occasional minute areas of cortical softening and foci of petechial hemorrhages.

The pituitary at times shows a moderate softening and a deep congestion of the pars anterior and of the infundibulum.. The landmarks are usually distinct.

The visceral changes are inconstant. In reference to the glands of internal secretion, usually no particular grossly definable alteration is noted. These glands participate in a universal congestion and moderate swelling, without characteristic pathologic change being regularly identified in any of them. The exception to this is the inconstant occurrence of the Waterhouse-Friderichsen syndrome wherein grossly definable destruction of the adrenals is noted.

Prominent microscopic changes are generally limited to the pituitary and adrenal glands. The outstanding changes in the pituitary are those of the posterior portion. In the posterior portion there is rather pronounced edema with considerable swelling, fragmentation of the fibers and formation of a loose spongy reticular pattern. In such areas, globules of eosinphilic material can be identified. The nuclei show various changes, particularly those of loss of chromatin material and fragmentation of the nuclear substance. The pars anterior presents usually a decided congestion and occasional interstitial edema. In 1 of the cases there was a focal area of eosinophilic necrosis. The adrenals in many of the acute cases show various degrees of hemorrhage, ranging from cases in which hemorrhage is limited to the zona reticularis to cases wherein all anatomic layers are destroyed by hemorrhage. In these cases there is no discernible adrenal tissue. In some of those in which hemorrhage is not too pronounced, the zona fasciculata layers show interstitial edema which is roughly outlined by columns of fasciculata cells. This gives a pattern resembling glandular formation. Various degrees of cellular swelling and degeneration are evident.

The pancreas is without persistent well defined change. Most prominent is that of irregular staining of the acini and moderate interstitial edema. The islets generally are moderately swollen, but the cells are well defined and have a usual position in the reticular pattern. In the few instances in which the thyroid gland has been studied there is prominent congestion of the interstitial tissue. The colloid and the epithelium are not constantly affected. The liver frequently shows moderate parenchymal cell swelling and granularity. This is accompanied with distended sinusoids in which moderate numbers of polymorphonuclear cells are seen. In only 1 instance was there any evident glycogenic change. In this case there was glycogenic vacuolization of the nuclei of the hepatic cells. The spleen usually exhibits a reticulum reaction of germinal centers. This is characterized by the

presence of minute chromatin granules and moderate hyperplasia, with increased activity of the germinal centers. The white pulp has variable changes, with congestion, thickening of the Billroth cords and changes in the plasma and polymorphonuclear cells. The kidneys and lungs are without distinct change. The myocardium generally shows interstitial edema, with occasional inflammatory cell foci limited to the interstitial tissue.

COMMENT

Soskin stated:

The differentiation of the various possible types of diabetes mellitus must await the development of adequate methods for the quantitative estimation of glandular function or of the titer of the various hormones in the blood. For the present all diabetic manifestations which are accompanied by a clinically recog-
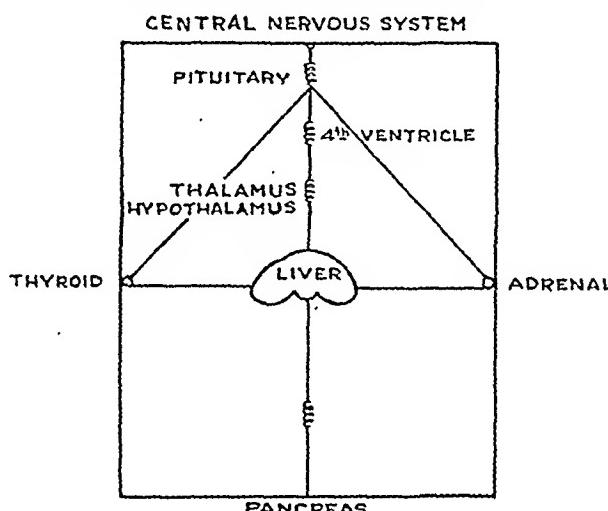
A modification of Soskin's [10] illustration, indicating the mechanical analogy to the endocrine balance as it affects the regulation of the blood sugar content by the liver.

nizable dysfunction of some gland or of the liver, are considered to be part of the syndrome associated with that clinical state.[10]

The accompanying figure is a modification of Soskin's diagram indicating a mechanical analogy to the endocrine balance as it affects the regulation of the blood sugar content by the liver.

The importance of hyperactivity of the pituitary gland lies in the fact that, as the recent studies of Price, Cori and Colwich [11] have clarified, anterior pituitary extracts control the rate of utilization of glucose by the body cells through a specific inhibition of the hexokinase enzyme system. The specific antagonist of this inhibiting substance is insulin,

10. Soskin, S.: Endocrine Disturbances in the Regulation of the Blood Sugar, Clinics 1:1286 (Feb.) 1943.

11. Price, W.; Cori, C., and Colwich, S. P.: The Effect of Anterior Pituitary Extract and of Insulin on the Hexokinase Reaction, J. Biol. Chem. 160:633 (Oct.) 1945.

which completely reverses the inhibition of the hexokinase system due to the presence of the anterior pituitary extract. The hexokinase enzyme system is indispensible because it catalyzes the first step in the utilization of glucose and is common to both glycogen formation and glucose oxidation. Thus, hyperactivity of the pituitary gland is capable of producing a transitory diabetic syndrome through an excessive secretion of the diabetogenic factor beyond that which can be counteracted by the specific antagonist, insulin.

These authors indicate that insulin acts by nullifying the effect of a specific inhibitor which originates in the anterior pituitary gland. If that was acceptable, then insulin would have no effect in the absence of the anterior pituitary gland. But experimentally it is known that the hypophysectomized animal is even more sensitive to insulin than is the normal animal. Hence this concept cannot be accepted for the present as an explanation of the pituitary as the sole cause of our findings.

As has been shown in the cases reported, the transitory diabetic state accompanying meningococcic meningitis subsides with the convalescence of the patient. However, as noted, it is evident that the pathologic process in this infection is characterized by its widespread involvement. It would be difficult to establish any one important site as an origin of the transitory diabetic syndrome. In the central nervous system it is evident that the thalamus, hypothalamus, anterior pituitary gland and the floor of the fourth ventricle are involved. The high incidence of meningococcemia and the malignant Waterhouse-Friderichsen syndrome would readily implicate the adrenal glands, but even the adrenal cortex or medulla is not necessarily alone responsible, for hepatic damage· may also contribute to this syndrome. It may be that there are different mechanisms in different cases, or there may be a combination of trigger mechanisms to set off these conditions. It is evident that the meningococcus causes a clinical disturbance in the endocrine regulation of the carbohydrate metabolism, which is the transitory diabetic syndrome. This minimal transitory hyperglycemia may indeed be misleading.

The liver, thyroid, spleen, pancreas, adrenals and heart may all participate in the accompanying disturbance of the base of the brain, so it is difficult to establish any one point of pathologic change as the. only recognizable etiologic factor. Minimal damage in the viscera may occur without any evidence of meningococcemia. In other cases, in our postmortem observations we have noted minimal damage to the brain but frank irreversible damage to the viscera, particularly the adrenals. Suggestion of intimate adrenal relationship in this syndrome is made ·because of: (a) infrequent finding of diabetes with Addison's disease, (b) hypoglycemia in adrenal apoplexy, (c) hyperglycemia produced by injection of epinephrine, (d) "diabetic" features of Cushing's syndrome

and pheochromocytomas of the adrenals and (e) failure to produce glycosuria experimentally with injury to the brain in cases wherein the splanchnic nerves supplying the adrenals have been sectioned.[12]

Table 2 records the total number of 233 patients treated. There were 58 patients with glycosuria, of whom 5 had been treated for diabetic acidosis.

A review of the series shows that this status exists in 24.9 per cent of 233 cases of meningococcic meningitis. This high frequency, unless combated by a high degree of anticipation, will result in an inexcusably

TABLE 2.—*Epidemic Meningitis at South View Isolation Hospital*

Year	Total Number of Cases	Number of Cases of Glycosuria	Number of Patients Treated for Diabetic Acidosis
1945	68	20	1
1944	125	31	1
1943	40	7	3
Totals	233	58	5

Per cent of total cases of glycosuria, 24.9

high percentage of error in diagnosis. The delay incurred while the diabetic acidosis alone is treated is extremely significant in the swift advance of the pathologic change to a state of irreversibility. Therefore, in all cases of coma, extensive examination and diagnostic procedures, such as lumbar puncture, must be instituted routinely.

SUMMARY

1. A transitory diabetic syndrome existed in 24.9 per cent of 233 cases of meningococcic meningitis.

2. Possible mechanisms are presented.

3. This condition subsides with the convalescence of the patient.

4. Five cases have been presented in which the patients were treated for diabetic acidosis.

5. Pathologic observations in 17 cases in which autopsy was performed are reviewed.

6. An accurate diagnosis may be seriously impeded by considering only the diabetic acidosis.

7. Extensive examination and diagnostic procedures, including lumbar puncture, should be carried out in all cases of coma.

12. Macleod, J. J. R.: Macleod's Physiology in Modern Medicine, edited by P. Bard, ed. 9, St. Louis, C. V. Mosby Company, 1941, p. 756.

INFECTIOUS · HEPATITIS

Report of an Outbreak, Apparently Water Borne

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THE GENERAL hospital in which I served during the war cared for 2,346 patients with infectious hepatitis in the course of a two year experience in the Mediterranean Theater. Of the 956 cases seen in the first three and one-half months, 680 involved British personnel admitted from a staging area which also furnished many cases of diarrheal disease. The parallelism between the incidence curves of diarrheal disease and infectious hepatitis was so close that it became the firm conviction of my associates and me that the answer to the question of causation of the latter disease was, in this instance at least, one of sanitation. We were forced to wait a year and a half, however, before an opportunity was offered to put our convictions to a clearcut test.

During April 1945 a number of patients with hepatitis with jaundice were admitted from one battalion of an infantry regiment in active combat on the Italian front. We were immediately struck by the fact that the great bulk of these patients came from either Company C or battalion headquarters. A survey of the wards of the three general hospitals in that area revealed the fact that there were, as of May 1, about 100 patients from this one battalion under treatment for hepatitis with jaundice. The distribution by companies was as follows: Company C 55, headquarters of the First Battalion 20, Company B 12, Company D 12 and Company A 1.

The onset of symptoms in every case except the one in Company A occurred between March 27 and April 17, 1945. The patient from Company A first began to have distress in the upper abdominal area on March 18 and, from the standpoint of epidemiology, possibly does not belong in this series.

In a review of the history of the battalion for the previous several months, the following facts were obtained: On March 3, 1945, after an attack beginning the day before, the battalion reached its objective, a ridge or series of ridges extending in a slight arc. They dug in as indicated in the drawing, with Company B on the left flank, Company

C in the center and Company A on the right. The men from Company D, the heavy weapons company, were scattered through all three areas. Battalion headquarters was at first located at point X, immediately in the rear of Company C. Several days later it was moved to a more sheltered position, near Company A. Some of the personnel, however, stayed on at point X.

The men in Company C and battalion headquarters, as long as they were there, obtained their drinking water from a well at point X. For the most part those in Company B got their water from a well close to their own position. A certain number of men from Company B, however, got water at point X whenever they were there to pick up packs or rations. The men in Company A and a few on the extreme right flank of Company C got their water from a well in the rear of Company A. The men of Company D got their water along with the men in each area. All supplies reached the various positions through the area occupied by Company A. The center and left flank of the position were exposed to cross fire, and there was, therefore, little incentive for personnel from Company A to venture in that direction.
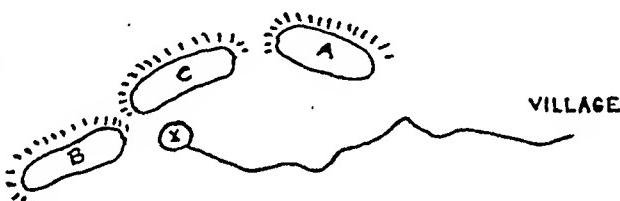
Location of companies A, B and C in relation to that of the polluted well (r).

About 75 of the patients in this series were interviewed, and only 1 (other than the man from Company A) claimed to have had no water from the well at point X. As nearly as we could determine it, the incidence of jaundice in those who did drink the water was about 1 out of 3. Except for the water we could find no essential difference between the conditions endured by Companies A and C. By talking to men who were wounded at this time, we learned that some men who had drunk as little as two canteens of the water became jaundiced. The amount of chlorination of the water was extremely variable and, in view of the work of Neefe,[1] is probably not of great importance.

This battalion was relieved on March 16, and Company I took over from Company C. We were at first puzzled as to why no cases of jaundice had appeared in Company I. Further questioning, however, revealed the fact that the well at point X had run dry on March 14 and that from then on the men in the center position of the line had to carry their water from either source A or source B.

1. Neefe, J. R.; Stokes, J., Jr.; Baty, J. B., and Reinhold, J. G.: Disinfection of Water Containing Causative Agent of Infectious (Epidemic) Hepatitis, J. A. M. A. **128**:1076-1080 (Aug. 11) 1945.

The epidemiologic evidence seemed to point so overwhelmingly to the well at point X as the source of the outbreak of hepatitis that a trip was made to the well on May 7. The party included an Italian medical officer and an officer from Company C, convalescent from hepatitis. Rain in the intervening weeks had again partially filled the well, so that it was possible to obtain enough water to fill ten previously sterilized 5 gallon (18,927 cc.) water cans. These were wired shut at the well and subsequently stored in the refrigerator at the hospital. The well was of a loose stone type of construction, and there was abundant evidence of fecal contamination of the ground immediately uphill from it. An Italian family living at the farm had been there for twenty-two years and claimed to have had no jaundice.

Routine bacteriologic study of the water showed it to be heavily contaminated with coliform organisms, but no pathogens were isolated either from the water itself or from the Seitz disks. Careful study of the residue on the Sietz disks also failed to reveal any amebic cysts. It therefore seemed reasonably safe to use the water, and permission was requested to run a feeding study on volunteers from our own detachment. This request was refused, and the unopened cans of water were shipped through channels to the United States. We have recently been informed that the water has not been used. In spite of the lack of absolute proof, it is felt that the epidemiologic data are sufficiently convincing to warrant its being reported as a water-borne outbreak.

COMMENT

The concept of polluted drinking water as a source of outbreaks of hepatitis is not new. In 1931 Fraser[2] reported a careful study of an institutional outbreak. One might well question the validity of the author's assumption that this outbreak was caused by Salmonella schottmülleri, but the epidemiologic evidence incriminating one water supply—an open spring—seems unassailable. Yenikomshian and Dennis in 1938[3] reported an outbreak of jaundice in a Lebanese village. In this instance, the epidemiology was by no means clearly worked out and the evidence pointing to the water supply could not be considered as anything more than suggestive.

In his final report on hepatitis in the Mediterranean Theater, Barker[4] called attention to a number of instances in which polluted

2. Fraser, R.: A Study of Epidemic Catarrhal Jaundice, Canad. Pub. Health J. **22**:396-411 (Aug.) 1931.

3. Yenikomshian, H. A., and Dennis, E. W.: An Outbreak of Epidemic Jaundice at Hamet, Lebanese Republic, Tr. Roy. Soc. Trop. Med. & Hyg. **32:** 189-196 (Aug.) 1938.

4. Barker, M. H.: Final Report on Infectious Hepatitis in Mtousa, p. 15 (confidential report).

drinking water seemed the probable source of an outbreak. During the summer of 1943, in one of the divisions staging in Africa the bulk of cases of hepatitis in the early stages were confined to two units whose conditions were in no way different from those in the remainder of the division except that they had a separate, common watering point. Again, in June 1944, essentially similar findings were obtained in relation to an outbreak in an engineer battalion in Algeria.

The only instance in which the opportunity to prove the case against polluted water was successfully seized is that reported by Neefe and Stokes in 1945.[5] These authors conducted an extremely careful study of an outbreak of hepatitis occurring in a summer camp. Added to a wealth of other data was the essential fact that water from one well produced in 4 of 5 volunteers a mild illness associated with hepatic dysfunction. Although overt jaundice developed in none of the 4, the study was so carefully controlled that the fact seems firmly established that their illness was caused by the same filterable agent demonstrated in the feces of patients in the outbreak.

If one accepts the epidemiologic evidence against water in this and other outbreaks and adds to it the resistance of the icterogenic agent to chlorination as established by Neefe,[1] the possibilities for bacterial warfare are enormous. They may well necessitate the development of entirely new methods of treating water in the field.

SUMMARY

1. An outbreak of infectious hepatitis in a combat unit is described.

2. Epidemiologic·evidence is given which seems to incriminate one polluted well as the source of the outbreak.

3. The military significance of this type of outbreak is indicated.

5. Neefe, J. R., and Stokes, J., Jr.: Epidemic of Infectious Hepatitis Apparently Due to Water Borne Agent: Epidemiologic Observations and Transmission Experiments in Human Volunteers, J. A. M. A. **128**:1063-1075 (Aug. 11) 1945.

AN UNUSUAL PULMONARY DISEASE

COLONEL JAMES C. CAIN

MAJOR EDWARD J. DEVINS

AND

LIEUTENANT COLONEL JOHN E. DOWNING

MEDICAL CORPS, ARMY OF THE UNITED STATES

WE WISH to describe a group of 26 cases of unusual pulmonary disease that occurred late in March 1944 in eastern Oklahoma. There is but one proved common factor, namely, every man who contracted the disease had spent some time in an abandoned storm cellar on the military reservation at Camp Gruber, Okla. (tables 1 and 2).

TABLE 1.—*The High Rate of Attack Among the Persons Who Entered the Storm Cellar* *

Date of Exposure	No. Exposed	Patients Requiring Hospitalization	Positive Signs and Symptoms of the Disease	Suggestive Signs and Symptoms of the Disease	Exposed but Not Available for Examination	No Disease	Definite Disease No.	Definite Disease %	Probable Disease No.	Probable Disease %	Possible Disease No.	Possible Disease %
								Total				
3/17/44	31	23	3	3	1	1	26	83.9	29	93.5	30	96.8
3/18/44	1	1	..	..	..	..	1	100.0	1	100.0	1	100.0
3/24/44	8	3	..	1	2	2	3	37.5	4	50.0	6	75.0
5/17/44	2	..	1	..	..	1	1	50.0	1	50.0	1	50.0
Total	42	27	4	4	3	4	31	73.9	35	83.3	38	90.4

* One patient hospitalized did not undergo the detailed tests. Therefore this study was made on 26 cases.

The group which was there on March 17 consisted chiefly of men from four squads, two squads from each of two companies. These companies lived in different camp areas, used separate messes and had never previously trained together. The men arrived at the area of the cellar around midnight and remained there until about 8 a. m., being in the cellar from three minutes to six hours. The morning of March 17 was clear and cold, but the ground was damp from rain of the two previous nights. The cellar was reasonably dry, and by covering the window and doorway with blankets the men were afforded the opportunity to smoke and build fires. The evidence suggests that the use of this particular cellar, in circumstances which apparently gave rise to the outbreak of disease, was a rather unique event.

Five civilians who had frequently visited and spent much time in the cellar five years previously, when the now demolished house was in use, gave no history of similar illness, and the roentgenograms of their thoraxes were entirely normal. Three civilians who had lived within 100 yards (92.3 meters) of the storm cellar were in perfect health and could not recall any similar illness among their families or friends. There had been no illness among their chickens, guinea fowl, dogs or other animals.

TABLE 2.—*Duration of Exposure and Severity of Clinical Signs in Twenty-Six Cases Studied in Detail*

Case	March 1944	Time in Storm Cellar	Evaluation of Severity	
			Clinical	Roentgenographic
1	17	5 hr.	Severe	Severe
2	17	3 hr.	Moderate	Mild
3	17	3 min.	Mild	Mild
	18	2 min.		
4	17	30 min.	Moderate	Moderate
5	17	6 hr.	Severe	Severe
6	17	3 hr.	Severe	Severe
7	17	6 hr.	Severe	Moderate
8	24	3 hr.	Mild	Mild
9	17	4 hr.	Severe	Severe
10	17	1½ hr.	Severe	Severe
11	18	5 min.	Mild	Mild
12	17	30 min.	Severe	Moderate
13	17	30 min.	Severe	Severe
14	17	5 hr.	Severe	Severe
15	17	6 hr.	Severe	Moderate
16	17	5 hr.	Severe	Severe
17	24	3 hr.	Mild	Mild
18	17	3½ hr.	Severe	Severe
19	17	5 hr.	Severe	Severe
20	17	2 hr.	Severe	Moderate
21	17	5 min.	Severe	Severe
22	17	4 hr.	Severe	Severe
23	17	6 hr.	Severe	Moderate
24	17	45 min.	Severe	Severe
25	17	30 min.	Severe	Severe
26	17	2 hr.	Severe	Severe

At no time had all the persons involved in the epidemic been together in one place except when in the cellar. None of the 31 men who visited the cellar was ill on the morning of March 17.

Among the men regularly assigned to the four squads that were stationed near the cellar on the morning of March 17, 7 did not participate in the problem. One additional man, a chauffeur, did not enter the cellar. None of these 8 men was admitted to the hospital or visited the dispensary during the period when the others became ill. Every fifth man from the two companies involved was questioned, and a roentgenogram of the thorax was made. None had signs or symptoms of the disease. A check of roentgenograms of the thorax in 100 cases of primary atypical pneumonia and tuberculosis occurring during this period revealed none similar to those of the affected men. Every man who became ill had been in the cellar, and none became ill who had not been in the cellar.

Examination revealed that neither the interior nor the exterior of the cellar was unusually damp or dusty. There was no evidence of animal burrows or droppings, ticks, fleas or any type of insect. A decomposing, maggot-infested opossum was found approximately 20 feet (6.1 meters) from the entrance. The opossum was superficially examined for the cause of death, but none was found. The advanced state of deterioration precluded autopsy.

The period of incubation for the patients who were admitted to the hospital was computed from the date of the visit to the cellar, as this was the only common factor in their histories. The average length
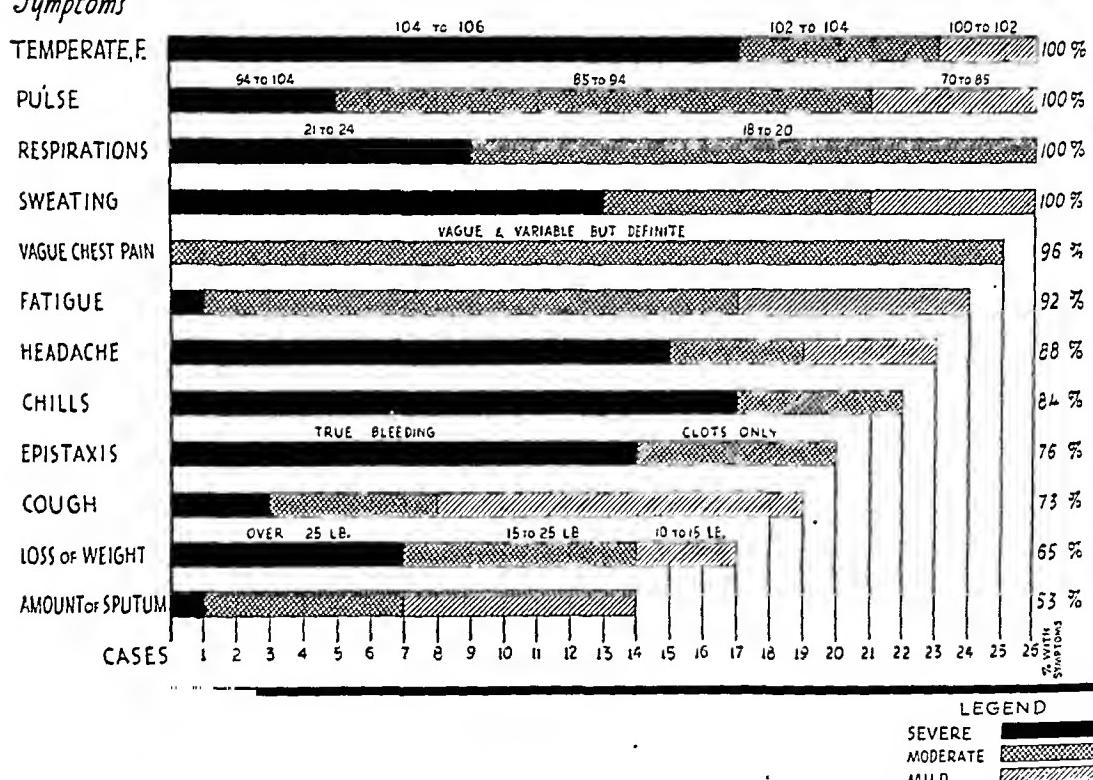
Fig. 1.—Consolidated chart of symptoms of 26 hospitalized patients.

of the period of incubation was 11.4 days. It ranged from eight to eighteen days, and it was ten days in 9 cases.

CLINICAL MANIFESTATIONS

Onset.—The onset of symptoms was sudden and characterized by general malaise, fatigue and muscular aching, followed within twenty-four to thirty-six hours by a chill (or chilliness), high remittent temperature, sweating, constricting pain in the thorax and epistaxis (fig. 1).

Temperature.—The temperatures varied from subnormal to 106 F.; the elevations followed no definite pattern of time. Only 1 of the

26 patients failed to have temperature above 101 F. Seventeen (65 per cent) of the patients had intermittent daily temperatures of more than 104 F. for a period of two to three weeks. At the end of eight weeks, 24 (92 per cent) of them occasionally had temperatures ranging from 99.4 to 101 F. These patients had temperatures of 99.2 to 100 F. after mild exercise throughout the illness. Prostration and malaise were not consistent with the temperature. It was not uncommon to find a patient with a temperature of 103 to 105 F. comfortably reading or writing a letter.

Pulse.—The pulse rate did not parallel the temperature. It ranged from 70 to 104 and averaged 88 per minute.

Respiration.—Nine (35 per cent) patients had respiratory rates of more than 20 per minute, and none had a rate of more than 25. The increase in the respiratory rate was not necessarily associated with elevation of temperature. In the third week there was mild reduction in the vital capacity; it then averaged 3.9 liters, and it increased in the eighth week of illness to an average of 4.3 liters. The most pronounced involvement of the lung tended to be associated with the most decided reduction in vital capacity, though in 2 of the 5 patients with mild and in 3 of the 7 with moderate attacks the degree of reduction was the same as that in the patients with severe attacks. In many instances attempts to measure the vital capacity were interrupted by coughing and constricting pain in the thorax.

Sweating.—Thirteen (50 per cent) of the patients complained of severe sweating, 8 (31 per cent) of moderate sweating and 5 (19 per cent) of mild sweating. Sweating was correlated to a large extent with the drop in temperature. Thirst was severe, and the patients drank large amounts of water. During the time when sweating was most striking, the erythrocyte count was frequently more than 5,000,000 per cubic millimeter. This observation suggested dehydration. Clinical manifestations of dehydration were absent, and the intake and output of fluid were adequate.

Pain and Aching.—Twenty-five (96 per cent) of the 26 patients complained of pain in the thorax. The pain was of two types: (1) substernal pain, constricting and pressing in character, and (2) a vague, variable, sharp pain located chiefly at the costal margins but sometimes occurring in any part of the thorax. The latter was usually of short duration (fifteen seconds to five minutes) and "sticking" in character. It was worse after exercise but not affected by deep inspiration. No friction rubs were present, nor was there any evidence of true pleurisy. The pain gradually diminished, but the sticking, sharp pain that occurred after exercise remained a major complaint during the entire period of hospitalization.

Fourteen (54 per cent) of the 26 patients complained of soreness and stiffness of the neck for as long as twenty-four weeks. Usually this was mild and transitory, but 1 ambulatory patient, not included in the 26 patients studied in detail, had stiffness of the neck which persisted for ten days as his chief complaint

Generalized aching was a complaint of 19 patients. It diminished in severity but was still a complaint of 7 patients in the third week of hospitalization.

Fatigue.—In these patients fatigue was a major complaint. Seventeen (65 per cent) of them complained of severe fatigue. They felt relatively well while resting but tired easily when called on to do any type of work. Fatigue was so pronounced that when patients were allowed to go on a pass they often returned early and remained in bed much of the following day. Fatigue persisted for seven months in many cases.

Chills.—Seventeen (65 per cent) of the 26 men had severe chills. Five (19 per cent) of the others had chilly sensations but no true rigors. Many had recurrent chills, lasting as long as sixty minutes, during the first week of the illness, and 3 (12 per cent) had them during the second week.

Headache.—Headache varied from dull frontal aching to severe, throbbing, sharp pain involving the entire head. The headaches of 15 (58 per cent) patients were severe, of 4 (15 per cent) moderate and of 4 (15 per cent) mild. Three (12 per cent) had no headache. The severity of the headaches gradually diminished, although they persisted for four weeks in 9 (35 per cent) cases. Salicylates and codeine sulfate were used as needed, but if the headache was severe even codeine did not afford complete relief.

Epistaxis.—Epistaxis occurred early in the disease and usually was not severe. Fifteen (58 per cent) patients had definite bleeding, and 5 (19 per cent) others blew clots from the nose. In every instance the patient stated that a nosebleed was unusual for him.

Cough.—Nineteen (73 per cent) patients coughed, but coughing was not a major symptom. Only 3 (12 per cent) had a severe cough, 5 (19 per cent) moderate and 11 (42 per cent) mild. Deep inspiration induced pain and coughing. In no case was coughing paroxysmal.

Sputum.—The cough was productive of some mucopurulent sputum in 16 (61 per cent) of the cases. Sputum was moderate in amount in 7 (27 per cent) and was never abundant. It had no unusual odor and contained no blood unless associated with epistaxis.

Loss of Weight.—Loss of weight during the first month of the illness was notable. Eighteen (69 per cent) of the patients each lost more than 10 pounds (4.5 Kg.). One patient lost 40 pounds (18.1 Kg.),

6 (23 per cent) lost 25 pounds (11.3 Kg.) or more, 7 (27 per cent) lost from 15 to 25 pounds (6.8 to 11.3 Kg.) and 4 (15 per cent) lost from 10 to 15 pounds (4.5 to 6.8 Kg.). During the first two to three weeks, the appetite was poor and practically all nourishment was taken in liquid form. No patient experienced vomiting or irregular bowel habits.

Miscellaneous Symptoms.—A few minor symptoms were noted. Eleven (42 per cent) patients complained of mild itching of the ventral surfaces of the wrists. This was associated with mild erythema at this site in 4 cases during the second week of illness. In most instances this lasted less than twenty-four hours. There was no generalized rash except for the urticaria noted in case 3 (table 2).

PHYSICAL EXAMINATION

Examination of the thorax revealed a striking paucity of clinical signs. Early in the disease scattered areas of dulness, diminished breath sounds and occasional moist, medium rales were reported in 8 (31 per cent) cases. Of these 8 cases, the disease appeared mild in 2, and on roentgenographic examination it appeared moderate in 1 and severe in 5. Deep breathing or coughing usually caused the rales to disappear. No pleural friction rubs were noted. A palpable spleen was present for a period of one week in 1 case (case 25). Effusions of the knee joint, for which aspiration was necessary, developed around the eighth week in 2 (8 per cent) cases (cases 2 and 7). The specific gravities of these synovial fluids were 1.020 and 1.022, and leukocyte counts were 4,200 and 6,000 per cubic millimeter respectively. The cultures were sterile. No other significant physical abnormalities were observed.

LABORATORY FINDINGS

Laboratory studies yielded little of significance. Leukocyte counts ranged from 5,600 to 14,600 cells per cubic millimeter, with 32 per cent to 86 per cent polymorphonuclear neutrophils. During the latter part of the illness there was a slight relative rise in the number of lymphocytes and monocytes, and in several cases the percentage of eosinophils increased to 6. Determinations of the hemoglobin content gave normal results. During the first two weeks, 14 (54 per cent) patients had erythrocyte counts of more than 5,000,000 and 3 (12 per cent) had counts of more than 6,000,000. The morphologic nature of the erythrocytes was normal. At some stage in the illness in each case the sedimentation rate of erythrocytes was from 30 to 50 mm. per hour (modified Cutler method) in all cases. In 10 (39 per cent) patients the increase occurred during the first week, in 12 (46 per cent) during the second week and in 1 during the third week. It returned to normal in all cases during the fourth and fifth weeks of illness.

Cultures of the blood of 14 (54 per cent) of the sickest patients during the first and second weeks of illness showed no growth. In case 16 five cultures were made at intervals of two hours on March 31 at the height of the illness. No yeast or fungi were isolated.

Forty-one examinations of sputum from the 16 patients from whom sputum was obtainable were made during the first week of the illness at the station hospital, Camp Gruber. Each examination showed gram-positive cocci in long and short chains and in pairs, as well as yeast forms identified as Candida (Monilia) albicans. Although the latter were numerous, they were merely one of a number of predominant organisms. The C. albicans was tested in mice, rats, rabbits, guinea pigs, opossums and monkeys and found to be only mildly if at all pathogenic.[1] No unusual tissue fibers were present in the sputum, and the cellular forms were not remarkable. Sputum from 7 (27 per cent) of the patients was sent to the Eighth Service Command Laboratory at Fort Sam Houston, Texas, where guinea pigs were inoculated. At necropsy of the guinea pigs six weeks later no pathologic change was found. Sputum from 2 patients (cases 23 and 26) was injected intraperitoneally into mice on April 14. The mice remained normal and showed no abnormality at necropsy. Cultures of material from their lungs were likewise sterile.

Repeated examinations of the urine of all the patients revealed nothing abnormal. The Kahn serologic test gave negative results in all cases. Agglutination tests in the first and third weeks for brucellosis and tularemia, the Weil-Felix (Proteus X19) test, the Frei test of the skin and a test of the skin for trichinosis gave negative results. Each of the last two tests was performed in 10 cases in the fifth week of illness.

The tuberculin test gave positive results in 2 of the 25 cases in which tests were made in the fifth week after onset. Serums from all patients, taken at approximately the third and eighth weeks of the illness, were studied for the antibodies of psittacosis, and ten specimens of serum (in cases 1 to 10) were examined for complement-fixing antibodies of lymphocytic choriomeningitis and agglutination of Leptospira icterohaemorrhagiae. All these studies gave negative results. Results of serologic studies for histoplasmosis were also negative.

Because of the high rate of attack and the similarity of the clinical picture to that of coccidioidomycosis, the possibility of the existence of this disease was thoroughly studied. Tests performed during the second week of the illness were made with fresh coccidioidin from army stock in a dilution of 1:100. All tests gave negative results. Complement

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1. See "Supplementary Report: Studies on the Causation of an Unusual Pulmonary Disease at Camp Gruber, Okla," which will be published later, for details of this work.

fixation and precipitin tests in 4 cases, however, did suggest possible coccidioidomycosis. Therefore, additional material for testing the skin —a 1 : 100 dilution of coccidioidin used in titrating and standardizing new batches of coccidioidin and a 1 : 100 dilution of antigen used for complement fixation—was utilized. In 4 (15 per cent) patients (cases 1, 7, 8 and 13; not those having positive reactions to serologic tests) the reaction to the former was positive but was only 1 plus.

Because of the finding of C. albicans in the sputum of each of the forty-one samples examined, this organism was considered as a possible although not probable etiologic agent. On May 16 seventeen specimens of sputum were obtained from the patients and eight specimens from men hospitalized for other diseases. These were examined carefully by the Commission on Acute Respiratory Diseases, Army Epidemiological Board, and the details of the study are discussed in the supplementary report. Even at this late date (May 16, 1946) 10 of the patients had sputums which contained C. albicans, while the sputum of none of the controls contained this organism. Materials for testing the skin were prepared, a C. albicans vaccine and a carbohydrate fraction of that organism being used. All 26 patients reacted with a 20 to 40 mm. area of erythema forty-five minutes after the material was injected. Of 19 control patients, 6 (32 per cent) had comparable positive reactions.

ROENTGENOGRAPHIC FINDINGS

Roentgenograms of the thorax were characterized by numerous small areas of infiltration, from 1 to 20 mm. in diameter, scattered diffusely and symmetrically throughout the fields of both lungs except for a tendency to spare the apexes and bases. In all cases the hilar lymph nodes were enlarged. These conditions were apparent a few days after the clinical onset of the disease and reached a maximal intensity within ten or twelve days. The mottled infiltrations remained static for about two months, after which time resolution became apparent. As the areas diminished in size they became more discrete and fibrotic, and by the sixth month the pulmonary fields showed a diffuse, fine fibrosis. From then on further change was imperceptible, and the fibrosis was considered to be permanent. The reduction in size of the hilar nodes to normal or near normal paralleled the decline of the infiltrated areas.

An attempt was made to evaluate the severity of the condition on the basis of involvement of the parenchyma and hilar nodes; in 15 (58 per cent) it was estimated as severe, in 6 (23 per cent) as moderate and in 5 (19 per cent) as mild.

REPORT OF CASES

CASE 16 (table 2).—*Severe Disease.*—A private 18 years old, who had been in the cellar for five hours on March 17, was admitted to the hospital on March 21,

1944 because of recurrent sycosis barbae. The lesions responded well to ammoniated mercury ointment and were practically clear by March 27. His past and family histories were noncontributory.

His illness began suddenly on March 28 while he was in the hospital. It began with an occasional nonproductive cough and pain in the thorax. The following day the cough persisted, a mild, throbbing, frontal headache developed and the temperature rose to 105 F. (fig. 2). Definite shaking chills were followed by notable sweating. During the first week there was mild, generalized aching, and mild epistaxis occurred on one occasion. Both types of pain in the thorax were present, as was fatigue of moderate degree. A mild cough, productive of a moderate amount of tenacious, grayish white sputum without unusual odor, persisted for two weeks.

The patient did not appear seriously ill or in evident discomfort. The respiratory rate ranged from 18 to 24 per minute. At the onset a few scattered moist

Fig. 2 (case 16).—Temperature chart. The disease was classified as severe. * indicates gram-positive cocci in long and short chains and in pairs and C. albicans. P indicates polymorphonuclear neutrophils; L, lymphocytes; M, monocytes, and B, basophils.

rales were heard over the posterior aspect of both lungs, but they were variable and disappeared with coughing or deep breathing. There was mild hyperemia of the nasopharynx. The blood pressure was 120 mm. of mercury systolic and 78 mm. diastolic. The cardiac rate was more than 110 per minute on only three occasions. These periods of mild tachycardia were not associated with decidedly elevated temperature. The remainder of the physical examination showed normality.

The erythrocyte count was 4,300,000 to 4,800,000 per cubic millimeter, and the value for hemoglobin was 90 to 95 per cent (Haden-Hausser method). The leukocyte count eight days prior to the onset of the illness was 6,000 per cubic millimeter of blood. The highest count occurred in the fourth week, when there were 12,800 leukocytes, of which 78 per cent were polymorphonuclear leukocytes and 22 per cent were lymphocytes. There were no abnormal cells. The specimens

of urine were consistently normal. The Kahn serologic test for syphilis elicited a negative reaction. The sedimentation rate of erythrocytes was 13 mm. per hour during the first week, 39 mm. during the second, 48 mm. during the third and 38 mm. during the fourth, and it returned to a normal rate of 8 mm. in one hour during the fifth week. Six cultures of the blood made during the first few days of the illness were sterile.

The Weil-Felix (Proteus X19) test and the agglutination tests for brucellosis and tularemia during the first and third weeks gave negative results. Sputum examined on April 3 and 5 contained gram-positive organisms in long and short chains and in pairs. C. albicans were seen in and isolated from each specimen. There was insufficient sputum for inoculation of guinea pigs. Complement fixation tests for psittacosis and coccidioidomycosis, agglutination tests for Weil's disease and precipitin tests for coccidioidomycosis gave negative results, as did tests of the skin for coccidioidcmycosis, trichinosis and tuberculosis.
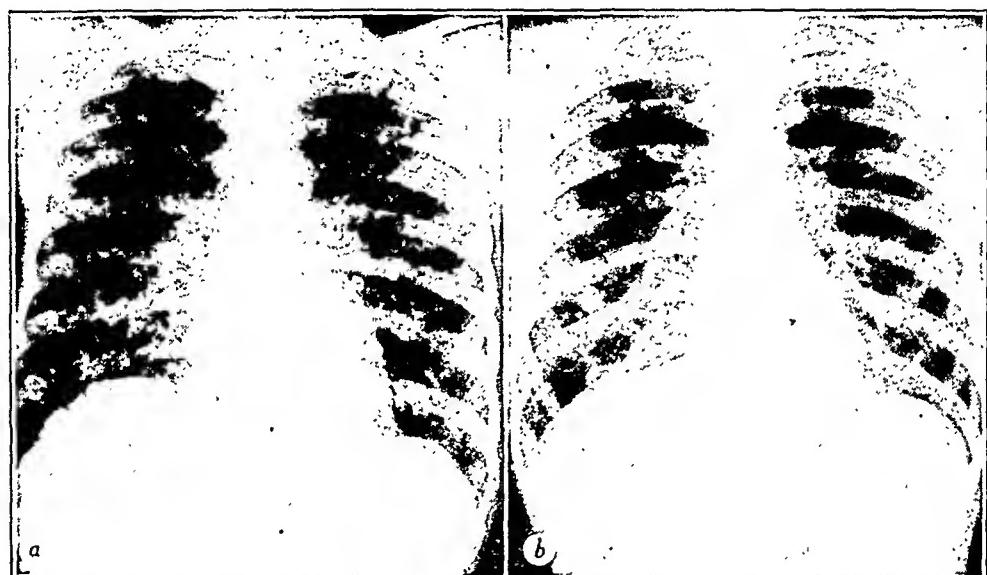
Fig. 3 (case 16).—Severe disease: a, on April 11, 1944, extensive mottled, 2 to 20 mm., areas of consolidation are noted throughout both pulmonary fields. b, on Oct. 26, 1944, evidence of clearing is noted, but persistent small fibrotic areas remain.

Bronchoscopy performed during the second week of illnesss revealed mild hyperemia of the bronchial mucosa. Washings of the bronchial tree with isotonic solution of sodium chloride were injected intraperitoneally into 3 mice. On May 3, 1 of the mice to which an injection had been given and a control mouse died. Necropsy revealed no cause of death in either. The 2 remaining mice showed no reaction and were found to be normal at necropsy two months later. Cultures of material from the lungs of the mice and of the washings of the bronchial tree showed no growth. The vital capacity was 4 to 4.4 liters during the illness. The electrocardiogram revealed nothing abnormal. The roentgenograms of the chest were startling (fig. 3 a). There were numerous small areas of dense, discrete consolidation scattered throughout the fields of both lungs, with slight sparing of the apexes and bases. The hilar lymph nodes were moderately enlarged.

The temperature, which was frequently elevated to more than 104 F. during the first week of illness, declined until it was essentially normal in the fourth week.

For about twenty-four weeks, however, it rose occasionally to around 99.5 F. The pain in the thorax diminished greatly in the first three months but recurred after exercise for the duration of hospitalization (seven and a half months). Fatigue, which was even more incapacitating, was equally persistent and decidedly increased by mild exertion. Roentgenograms of the thorax revealed gradual clearing; the areas of consolidation became smaller and fibrotic in character (fig. 3 b). These areas underwent so little, if any, change in the last few months of the illness that they were assumed to be permanent.

CASE 15 (table 2).—*Moderate Disease.*—The patient, a private 18 years old, who had been in the cellar for six hours on March 17, began to have chilliness, muscular aching, malaise and fever on March 27. A mild cough, productive of a moderate amount of mucoid, grayish white sputum without unusual odor, developed, and it persisted for two weeks. The temperature on the patient's admission to the hospital was only 99.4 F. Headache was severe and primarily in the frontal region, varying from a dull aching sensation to a sharp, throbbing pain. Sweating was severe. The patient had chilly sensations but no true chills. Mild expistaxis occurred on two occasions. Pain in the thorax varied from a constricting type of distress to a sharp, sticking pain. The former was located primarily in the substernal region, and the latter frequently involved the costal margins.

The patient's past and family histories were noncontributory. The systolic blood pressure was 122 mm. of mercury and the diastolic 60 mm. The skin was hot, and the nasal and pharyngeal mucosa showed moderate congestion. The lungs were clear on percussion and auscultation. Results of the remainder of the physical examination were not significant.

The erythrocyte count ranged from 4,100,000 to 5,600,000 cells, the concentration of hemoglobin was from 90 to 95 per cent (Haden-Hausser method) and the leukocyte count was from 8,100 to 14,600 cells per cubic millimeter of blood. The differential count averaged 60 per cent neutrophils, 38 per cent lymphocytes and 2 per cent eosinophils, with no abnormal cells. During the fifth week the eosinophils increased to 6 per cent. The urine, examined on numerous occasions, was always normal. The sedimentation rates (modified Cutler method) were 13 mm. per hour in the first week, 45 mm. in the second, 43 mm. in the third, 18 mm. in the fourth and 4 mm. in the fifth. Cultures of the blood made during the first week of illness were sterile. The Kahn test, agglutination tests for brucellosis and tularemia and the Weil-Felix (Proteus X19) test gave negative results. Examinations of sputum on April 2, 3, 4 and 5 showed gram-positive cocci in long and short chains and in pairs and C. albicans. Inoculation of guinea pigs with sputum, complement fixation tests for psittacosis and coccidioidomycosis, a precipitin test for coccidioidomycosis and repeated tuberculin, coccidioidin and trichinin tests of the skin gave negative results. The vital capacity was 3.4 to 3.6 liters throughout the illness. An electrocardiogram revealed nothing abnormal. Roentgenograms of the chest showed many small, 2 to 20 mm., discrete areas of consolidation and enlargement of the hilar lymph nodes. The areas of consolidation were definite and prominent but fewer than in the patients whose illness was classified as severe.

This patient was 1 of 5 who were treated with sulfadiazine for seven days. No change was noted with this therapy. Headaches and fatigue persisted through the fourth week, and the temperature was essentially normal by the fifth week. At the end of seven and a half months the patient still complained of weakness, constricting pain in the thorax and general malaise. Improvement in the roentgenograms of the thorax paralleled that found in case 16, and seven and a

half months after the onset of illness the areas of consolidation were replaced by a fine, diffuse fibrosis, which appeared permanent.

CASE 3 (table 2).—*Mild Disease.*—A private first class, 18 years old, was admitted to the hospital because of acute illness. He complained of chilliness, fever and headache. He was in the cellar for three minutes on March 17 and two minutes on March 18. At the age of 10 years he had had empyema of the left side of the thorax, for which surgical drainage was carried out. Recovery was prompt, and his subsequent health, except for frequent attacks of "hives," was excellent until this admission to the hospital. The family history was irrelevant.

On April 1 headache, chilly sensations and generalized aching developed and were followed shortly thereafter by nasal congestion and a slight, nonproductive cough. The headache was frontal and throbbing and of moderate severity. The next day the patient experienced a severe nosebleed. All symptoms continued and became worse until his admission on April 3, when the temperature was 100.4 F.
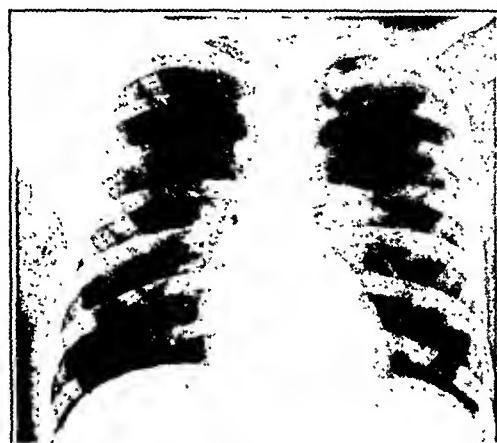
Fig. 4 (case 3).—Mild disease at the height of the patient's illness on April 17, 1944. Enlargement of hilar nodes only may be noted.

Physical examination revealed a well healed thoracotomy scar posteriorly on the left side. The lungs were clear on percussion and auscultation. The systolic blood pressure was 124 mm. and the diastolic 78.

The leukocyte count ranged from 7,750 to 8,600. The differential count was within normal limits, and there were no abnormal cells. The erythrocyte count remained around 5,000,000 and the value for hemoglobin (Haden-Hausser method) was 90 per cent. The sedimentation rate of erythrocytes (modified Cutler method) was 34 mm. per hour the day after the patient's admission; it declined to 8 mm. three weeks later. All the special tests performed in the other cases were carried out, but the results were negative. The vital capacity was 3.7 liters, 3.9 liters and 4 liters in the third, eighth and twenty-sixth weeks of illness respectively. The electrocardiogram revealed normal conditions. There was no sputum for examination. Roentgenograms of the chest showed enlargement of the hilar lymph nodes, but the parenchyma of the lung was normal (fig. 4).

Only supportive treatment was given. On several occasions during hospitalization transient attacks of generalized papular urticaria developed. These lasted less than half an hour and disappeared without treatment. These attacks were of an unknown cause and had been noted by the patient for many years. They caused only mild discomfort and were not influenced by his illness. Profuse epistaxis was a daily occurrence for a few weeks. In the early weeks of the illness

the patient had only slight dry cough and no pain in the thorax. The symptoms improved gradually during the second and third weeks of illness coincident with a decline in temperature. In a period of four months the hilar nodes gradually returned to normal size. Seven and a half months after the onset of illness, the only complaints were weakness and fatigue, which were easily precipitated by mild exertion.
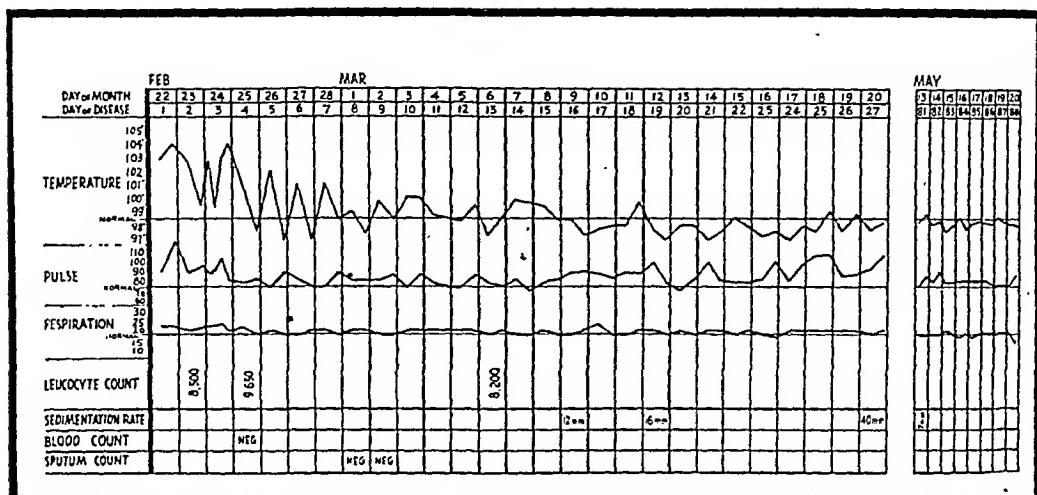
Fig. 5.—Temperature chart of the patient in a case in the 1943 outbreak.
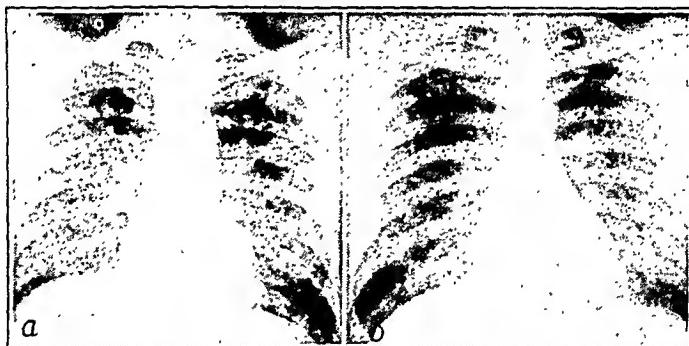
Fig. 6.—The lungs of a patient during the epidemic in 1943. *a,* on February 27 extensive, 2 to 10 mm., areas of consolidation and enlargement of hilar lymph nodes are present. *b,* on April 6, 1944 there is definite improvement, but fibrotic areas persist.

SIMILAR OUTBREAK IN 1943

During the latter part of February 1943, 5 soldiers had been admitted to the same hospital with signs and symptoms practically identical with those of the 1944 group. When the 1944 outbreak occurred, it seemed to resemble the condition which we had studied in 1943. Review of the records and roentgenograms revealed that clinically and roentgenographically the cases in the two outbreaks were indistinguishable (figs. 5 and 6). Three days prior to admission to the hospital all these men

had been subject to an extremely high concentration of dust while driving over new roads at the end of a long convoy. Examination of dirt from the road showed the silica content to be not unusually high, and no unexpected minerals were found. No history of their having been in the cellar was obtained. One of the 5 men was available for reexamination and a year after his attack showed roentgenographic evidence of the disease. The etiologic factor of this outbreak was not determined.

DIFFERENTIAL DIAGNOSIS

In the 26 cases in which the patients were under our observation and the 5 cases in the 1943 outbreak the clinical syndrome was distinct from other forms of pneumonia studied at Camp Gruber. The signs and symptoms that differentiate the disease from primary atypical pneumonia are the sudden onset, the severe and prolonged clinical course and the disseminated lesions in the roentgenograms of the thorax.

The explosiveness and severity of the disease raised the question of psittacosis, but the absence of any history of exposure to birds, the lack of evidence of large areas of pulmonary consolidation in the roentgenograms, the negative results of the complement fixation tests and the fact that all the patients recovered do not support this diagnosis.

Rickettsial infections must be considered, though there was no history of insect bites, only a mild rash on the wrists of 3 patients and no evidence of disseminated systemic infection in any organ other than the lungs. Serologic tests showed the serums of 10 patients to be negative for Q fever.

Results of serologic studies for histoplasmosis were negative. The diagnosis of coccidioidomycosis was excluded by the occurrence outside a recognized endemic region, the absence of cavitation or of secondary dissemination in any case and the negative reactions to coccidioidin tests. Only 4 of the 26 patients had positive cutaneous reactions, and these reactions were only 1 plus. Complement fixation and precipitin tests for coccidioidomycosis gave results suggestive of the disease in only 4 cases.

The presence of C. albicans during the first week of the illness in forty-one specimens of sputum from the 16 patients from whom sputum was available and the failure to find even one early specimen of sputum that did not contain this organism certainly suggests it as a possible etiologic agent. Even during the second month ten out of seventeen specimens of sputum from these men contained C. albicans, and sputum from none of the 8 controls contained the organism. The uniformly positive reactions to the tests of the skin were further evidence pointing toward moniliasis. However, due to the lack of supporting immunologic evidence, it is questionable that this was the cause of the disease.[1]

Wylie and DeBlase [2] have recently reported a case of bronchopulmonary moniliasis that resembles our cases. The roentgenographic findings in their case were somewhat similar to those in our series, except that enlargement of the hilar nodes, an outstanding symptom in our cases, was not noted. The scarcity of productive cough, the absence of rales, the short period of incubation and the lack of dyspnea in our cases are other distinct differences.

Idstrom and Rosenberg [3] have recently described a respiratory disease that occurred at Camp Crowder, Mo. This disease was found in 40 patients and was classified as primary atypical pneumonia. It appeared among men detailed to squads for clearing abandoned houses, barns and chicken coops. The roentgenographic findings consisted in accentuation of hilar shadows, peribronchial infiltration and generalized, patchy, parenchymal infiltrate, which had a tendency toward localization. No fatalities occurred, and there were no complications other than persistent malaise and weakness. Idstrom visited Camp Gruber, and the records and roentgenograms of his cases were reviewed. In 4 the symptoms were indistinguishable from those in the cases at Camp Gruber. In the remainder the data were less characteristic, the condition was milder and extensive mottling throughout the parenchyma of the lungs was not present. Clinically the cases were similar, but most of the patients had a shorter illness. It is probable, however, that the cases occurring in Camp Crowder were similar to if not identical with the cases at Camp Gruber. Idstrom and Rosenberg determined no specific etiologic agent.

The possibility exists that the disease was not due to an infectious agent but rather to the inhalation of some irritant. Pneumoconiosis and bagassosis [4] might be mentioned as examples. However, the sudden onset, prolonged fever of a severe degree and elevated sedimentation rates favor the existence of an infectious agent.

SUMMARY

A severe outbreak of an unusual form of pulmonary disease occurred at Camp Gruber, Okla., in March 1944. The epidemiologic evidence pointed to a single common exposure in a storm cellar. The rate of attack was extremely high. The disease was characterized by severe constitutional symptoms, absence of physical signs and diffuse infiltration of the parenchyma of the lung, which took on a discrete, chronic, fibrotic

2. Wylie, P. E., and DeBlase, J. A.: Bronchopulmonary Moniliasis, J. A. M. A. **125**:463-465 (June 17) 1944.

3. Idstrom, L. G., and Rosenberg, B.: Primary Atypical Pneumonia, Bull. U. S. Army M. Dept., October 1944, no. 81, pp. 88-92.

4. Sodeman, W. A., and Pullen, R. L.: Bagasse Disease of the Lungs, Arch. Int. Med. **73**:365-374 (May) 1944.

appearance in the roentgenogram. Recovery was slow and incomplete. At the end of seven and a half months, 5 of the original 26 patients who had mild disease had returned to duty and 21 had required separation from the service. These 21 still complained of severe fatigue, weakness and pain in the thorax following even mild exercise. A definite causative agent was not determined. Similar cases occurred at Camp Gruber in February 1943.

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1945 to July 1946

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The publications during this period reflect the transition from military to civilian life. A few papers are based on wounds received in combat; a number deal with studies made in military hospitals and emphasize again the role of gastrointestinal disease, particularly bacillary dysentery, in the armed forces and a few on parasitic diseases are based on military experiences in the tropics and endemic areas. The majority, however, are the usual studies of peacetime. While it is evident that active investigation has been continued throughout the war, it nevertheless seems probable that with the return of large numbers of men to the universities, medical colleges, hospitals and laboratories, the quantity and quality of papers published in succeeding years will rise sharply.

GENERAL PAPERS AND REVIEWS

The roentgenologic phases have been reviewed separately and need not be repeated here,[1] nor will books be discussed.[2]

The incidence of gastrointestinal disorders has been studied in both civilian and military installations. Emery's analysis of 2,839 patients includes an analysis of 1,000 consecutive patients from the wards of the Peter Bent Brigham Hospital, 1,000 consecutive outpatients, 839 patients from a general practice and reports of 500 consecutive autopsies.[3] Of the total, 19 per cent had applied for the relief of gastrointestinal symptoms; 50 per cent of these had organic disease in the accepted sense of the word. The incidence of organic disease was greatest in the patients in the wards, less in outpatients and lowest in the private patients.

Of 121 cases of chronic dyspepsia thoroughly studied in the Mediterranean Theater in 94, or 70 per cent, the condition was classified as psychoneurosis.[4] Some form of gastritis was present in 46 per cent of the total and in 60 per cent of the psychoneurotic patients. In 14 cases of acute hepatitis with prolonged dyspepsia, evidence of continued hepatic dysfunction was present in only 1. A diagnosis of psychoneurosis was made for 11 patients, and 3 others had organic diseases, e. g., duodenal ulcer, amebiasis and secondary syphilis. Of 41 admitted with the diagnosis of chronic hepatitis without jaundice, the laboratory findings were compatible with chronic hepatitis in 4 of 30 diagnosed as having psychoneurosis, the edge of the liver was palpable in 11 and the spleen was palpable in 7 (tertian malaria). Of 31 admitted with a diagnosis of peptic ulcer, only 3 had a roentgenologically demonstrable ulcer. Six patients with recurrent chronic diarrhea and palpable liver

1. Gilbertson, E. L., and Kirklin, B. R.: A Review of the Literature on Roentgenology of the Gastro-Intestinal Tract for the Year 1944, Gastroenterology **6:**112-129, 1946.

2. Farrell, J. T., Jr.: Roentgen Diagnosis of Diseases of the Gastrointestinal Tract, Springfield, Ill., Charles C Thomas, Publisher, 1946. Green, H. W., and Watkins, R. N.: Appendicitis in Cleveland, Cleveland Health Council, 1946. Held, I. W., and Goldbloom, A. A.: Peptic Ulcer: Diagnosis and Treatment, Springfield, Ill., Charles C Thomas, Publisher, 1946. Spiesman, I. E.: Essentials of Clinical Proctology, New York, Grune & Stratton, Inc., 1946. Vahlne, G.: Serological Typing of the Colon Bacteria with Special Reference to the Occurrence of B. Coli in Man Under Normal and Pathological Conditions Particularly in Appendicitis, Acta path. et microbiol. Scandinav., 1945, supp. 62. Fantoni, V. J.: La eosinophilia en el contenido de los apendices en las oxiurosis apendiculares, Rosario, Argentina, Musumarra and Cia, 1945. Hirschberg, F.: Diagnostik und Therapie der Magen-Darmerkrankungen in zwölf Vorlesungen, Copenhagen, Ejnar Munksgaards, Forlag, 1946.

3. Emery, E. S., Jr.: The Incidence of Gastrointestinal Disorders from a Study of 2,839 Cases, Gastroenterology **6:**477-492, 1946.

4. Schwartz, I. R., and Perlmutter, M.: Chronic Dyspepsia in the Mediterranean Theater, Gastroenterology **6:**21-34, 1946.

were thought to have psychoneurosis. Psychoneurosis was the commonest diagnosis made for patients with chronic dyspepsia with vague abdominal symptoms. While we are not inclined to minimize either the incidence or the significance of psychiatric states in patients with gastrointestinal complaints, it nevertheless seems to us erroneous to classify all "functional disorders" as psychoneurosis.

Wylie[5] did not find any significant difference in the incidence of upper gastrointestinal disease in the American and German armies.

Culver[6] reports 4 instances of miliary pulmonary metastases from primary carcinoma of the gallbladder, hepatic duct, stomach and pancreas, respectively. Of 168 cases of metastatic carcinoma of the bony skeleton there were 11, or 6 per cent, in which the disease was gastrointestinal in origin.[7]

ESOPHAGUS

Esophageal disease has been reviewed by Benedict[8] and McKay.[9]

Incidence of Esophageal Disease.—Vinson[10] compares the diseases of the esophagus in a group of 393 white men with those in 130 Negroes. Carcinoma was found in 67 white and in 24 Negro patients, cardiospasm in 58 white persons and in 16 Negroes, foreign bodies in 142 white patients and in 40 Negroes and esophageal varices in 4 white patients and in no Negroes; there was 1 Negro patient with polyposis.

Johnstone[11] analyzes the nonmalignant causes of dysphagia. In patients in the first decade of life, congenital atresia, congenital stricture, web, shortening and spasm may be noted; in patients in the second decade, simple stricture on the basis of congenital stenosis; in patients in the third decade, achalasia; in patients in the fourth and fifth decades, postcricoid web, and in those in the fifth to seventh decades, peptic ulceration and partial thoracic stomach. Pharyngeal diverticulum is most frequent in the sixth decade. Leiomyoma and fibroma are the predominating benign tumors.

5. Wylie, P. E.: Incidence of X-Ray Evidence of Upper Gastro-Intestinal Pathology in German Prisoners of War, Mil. Surgeon **98**:125-131, 1946.

6. Culver, G. J.: Miliary Carcinosis of the Lungs Secondary to Primary Cancer of the Gastro-Intestinal Tract, Am. J. Roentgenol. **54**:474-482, 1945.

7. Thomas, G. L.: Metastases to Bone in Gastrointestinal Malignancy, S. Clin. North America **26**:692-694, 1946.

8. Benedict, E. B.: Esophagus: Review of Literature for 1944, Gastroenterology **5**:18-26, 1945.

9. McKay, J. W.: Radiological Diagnosis of Certain Diseases of the Lower Esophagus, S. Clin. North America **26**:306-318, 1946.

10. Vinson, P. P.: Incidence of Esophageal Disease in Negroes, South. M. J. **38**:452-453, 1945.

11. Johnstone, A. S.: Dysphagia Due to Causes Other Than Malignant Disease, Edinburgh M. J. **53**:160-172, 1946.

Atresia and Tracheoesophageal Fistula.—Progress in the treatment of this congenital anomaly is indicated by the report of another infant submitted to successful surgical intervention.[12]

Pulsion Diverticulum.—Bortone [13] prefers the two stage method of excision.

Esophageal Displacement.—Epstein,[14] in 6 patients with advanced left atrial dilatation due to rheumatic mitral and aortic valvular disease, noted esophageal displacement toward the left and posteriorly, closely following the transverse and descending thoracic aorta. The atypical position of the esophagus is attributed to aortic-esophageal adhesions.

Short Esophagus.—In the judgment of Smithers,[15] the majority of conditions diagnosed as short esophagus roentgenologically are instances of hiatus insufficiency associated with spasm of the longitudinal muscle fibers, resulting from irritation of the esophagus by gastric juice regurgitated because of a lax hiatus which is developmental in origin or due to loss of elasticity of the tissues in later life. True short esophagus is seldom found at postmortem examination.

Esophagitis and Peptic Ulcer.—Steiner [16] gives a good review of the mechanisms involved in the development of chronic ulcerative esophagitis. Two esophageal ulcers were noted by Coventry and Wells [17] in 2,500 consecutive autopsies over a ten year period. Additional conditions are reported,[18] including an extremely rare perforation of an ulcer into the left auricle.[19] Preiskel [20] describes a perforation into the mediastinum, with ultimate recovery, the first to be reported in the literature.

12. Gross, R. E., and Scott, H. W., Jr.: Correction of Esophageal Atresia and Tracheo-Esophageal Fistula by Closure of Fistula and Oblique Anastomosis of Esophageal Segments, Surg., Gynec. & Obst. **82**:518-526, 1946.

13. Bortone, F.: Esophageal Diverticulum, Am. J. Surg. **70**:64-67, 1945.

14. Epstein, B. S.: Atypical Esophageal Displacement with Left Atrial Dilatation, Am. J. Roentgenol. **54**:262-269, 1945.

15. Smithers, D. W.: Short Esophagus (Thoracic Stomach) and Its Association with Peptic Ulceration and Cancer, Brit. J. Radiol. **18**:199-208, 1945.

16. Steiner, G.: Chronic Ulcerative Esophagitis with a Report of a Case of Ulcer in Esophageal Varices, Brit. J. Radiol. **19**:145-152, 1946.

17. Coventry, W. A., and Wells, A. H.: Chronic Peptic Ulcer of the Esophagus, Minnesota Med. **28**:729-733, 1945.

18. Diaz, F., and Riera, M.: La úlcera péptica del esófago, Rev. méd. de Chile **73**:1053-1059, 1945. Hertzog, A. J., and Leighton, R.: Spontaneous Perforation of the Esophagus, Minnesota Med. **29**:442, 1946.

19. Johnstone, A. S.; Harper, R. A. K.; McLaren, J. W., and Grossman, M. E.: Non-Malignant Conditions of the Esophagus: A Symposium, Brit. J. Radiol. **19**:101-117, 1946.

20. Preiskel, E.: Peptic Esophageal Ulcer: Non-Fatal Perforation, Lancet **1**:497-498, 1946.

Scleroderma.—In 36 of approximately 350 cases of scleroderma or acrosclerosis reviewed by Olsen, O'Leary and Kirklin,[21] dysphagia occurred or lesions of the esophagus were demonstrated. In 18, positive roentgenographic or endoscopic evidence was present. Dilatation of the esophagus, similar to that seen in cardiospasm, was observed in 7 cases and hiatal hernia with intrathoracic stomach in 9. In 2 others sclerodermic changes were demonstrated in the esophageal wall. Thirty-three of the 36 presented the clinical syndrome of acrosclerosis; all the 18 patients with conclusive roentgenographic or endoscopic evidence had definite acrosclerosis. Repeated dilatations over prolonged periods gave moderate relief. Two additional cases are reported by Rafsky and Herzig.[22]

Cardiospasm.—Scott[23] gives an excellent review of cardiospasm, dividing it into four types requiring different modes of therapy: (1) achalasia, the commonest, usually treated successfully by dilation; (2) true cardiospasm due to a reflex irritation, requiring location and removal of the focus; (3) partial constriction near the cardia, which is rarer, and (4) dolichoesophagus, requiring surgical correction. In the first two types spinal anesthesia relaxes the cardia, enabling the esophagus to empty promptly; in the third and fourth it has no effect. Reports of 2 cases are of interest in this connection. Fleminger and Smith[24] describe a 16 year old girl, previously healthy, in whom, following fracture of the right cerebellar fossa with underlying extradural hematoma, persistent and total dysphagia developed. Attempts to cure by suggestion, even with the intravenous use of sodium amytal, were unsuccessful. Fluoroscopy revealed achalasia of the cricopharyngeal muscle and of the cardiac sphincter of the esophagus. Inhalation of one ampule of octyl nitrite was followed by an immediate and permanent recovery of normal swallowing. Lewsen[25] refers to an obviously inadequate, immature, hysterical person, with dysphagia and dyspeptic complaints since infancy, who joined the army during a remission and broke down in combat. The response to nitrite was poor, but he improved rapidly with the use of a mercury bougie. The condition is interpreted as cardiospasm of psychic origin cured by mechanical measures. The validity of

21. Olsen, A. M.; O'Leary, P. A., and Kirklin, B. R.: Esophageal Lesions Associated with Acrosclerosis and Scleroderma, Arch. Int. Med. **76**:189-200 (Oct.) 1945.

22. Rafsky, H. A., and Herzig, W.: Scleroderma with Oesophageal Symptoms, Gastroenterology **6**:35-39, 1946.

23. Scott, W. J. M.: Idiopathic Dilatation of the Esophagus, Ann. Surg. **122**:582-605, 1945.

24. Fleminger, J. J., and Smith, M. C.: Achalasia of Esophagus Following Depressed Fracture of Base of Skull, Lancet **1**:381-383, 1946.

25. Lewsen, S. C.: Achalasia of the Esophagus, Letters to the Editor, Lancet **1**:479, 1946.

the diagnosis is not well established, and the psychotherapy of the mechanical procedure is ignored. This is one of 2 instances in which dysphagia was the primary symptom encountered by Lewsen in 6,000 soldiers with acute and chronic psychoneurosis during a three year period. In the second instance the patient had suffered two esophageal strictures after swallowing a glass of "chianti" proffered by an Italian villager. Therapy with nitrites, further reassurance and persuasion and abreaction (but no bougie) enabled him to eat solids to a moderate degree. This is interpreted as a restoration of function after psychiatric treatment; it should not be confused with cardiospasm, and it does not constitute proof that psychotherapy influenced the strictures but merely that it influenced the patient's reaction to the strictures.

Robson and Wilkinson[26] describe an instance of achalasia subsequently proved at autopsy relieved clinically at first by inhalations of octyl nitrite; as tolerance to the drug developed, its effectiveness was lost. We have been pleased with the effect of octyl nitrite in many patients, particularly in those with mild symptoms of short duration; Johnstone, Harper, McLaren and Grossman[19] report two satisfactory responses. However, patients with long-standing or severe symptoms or with high grade esophageal dilatation may not obtain relief.

Clagett and others[27] reported 4 cases of cardiospasm treated successfully with esophagogastrostomy. A good functioning result was obtained despite the fact that the esophagus remained dilated after operation. A similar procedure was used by Clark and Adams[28] in 5 cases of benign stricture of the lower part of the esophagus, with no deaths and complete relief of symptoms. An interesting Soviet report describes 24 patients in all age groups with cardiospasm subjected to operative intervention by so-called transdiaphragmatic mediastinotomy.[29] An inflammatory process of varying intensity was found in the areolar tissue of the mediastinum, involving the diaphragm, the vagus nerve and the esophagus proper. The esophageal inflammation is considered secondary to inflammation of unknown origin in the mediastinum and infradiaphragmatic space. Cardiospasm is thus attributed to mediastinitis, with irritation and spasm of the diaphragm, crurae and paraesophageal muscles; scar tissue makes the constriction permanent. American readers will require further evidence before they accept this theory. Treatment, described as satisfactory, consisted in transdiaphragmatic mediastinotomy

26. Robson, T., and Wilkinson, R. S.: Tolerance to Octyl Nitrite in Achalasia of the Cardia, Lancet **1**:737-738, 1946.

27. Clagett, O. T.; Moersch, H. J., and Fischer, A.: Esophagogastrostomy in the Treatment of Cardiospasm, Surg., Gynec. & Obst. **81**:440-445, 1945.

28. Clark, D. E., and Adams, W. E.: Transthoracic Esophagogastrostomy for Benign Strictures of the Lower Esophagus, Ann. Surg. **122**:942-953, 1945.

29. Savinykh, A. G.: Esophagogastrostomy for Cardiospasm, Am. Rev. Soviet Med. **3**:292-319, 1946.

and resection of the diaphragmatic crura, with sympathetic denervation of the medial diaphragm and subdiaphragmatic area combined with bilateral vagotomy and followed later by esophagogastrostomy.

Carcinoma.—Boros [30] reviews 332 cases encountered from 1922 to 1944. In the majority the symptoms were of less than one year's duration; 88 per cent of the patients were males, and the highest incidence occurred in patients in the fifth decade. The lesion in 70 was in the upper third of the esophagus, in 142 in the middle third and in 120 in the lower third. Dysphagia, pain, loss of weight, vomiting, hoarseness, bleeding and coughing were the most prominent symptoms in the order named; 34 had fever. In 80 patients given radiation therapy the average length of life after treatment was three to six months. In 168 treated by gastrostomy the same duration of life (three to six months) was obtained. The operative mortality was 25 per cent. Seven patients were subjected to exploration (thoracic), and in all the lesion was inoperable (metastases). Two perforations of the aorta due to carcinoma of the esophagus are reported.[31]

There are two reports dealing with the surgical treatment of esophageal cancer. In twenty radical resections by Sweet [32] of lesions located in the midthoracic portion, a high esophagogastric anastomosis in the vicinity of the aortic arch was performed and regional lymph nodes were removed. In 8 the anastomosis was below the aortic arch; in 12 it was above the arch, the esophagus being relocated. There were 6 deaths, a mortality of 30 per cent. In 24 of Clagett's [33] 54 cases the lesions were inoperable; in 30 transthoracic resection was possible. In 27 the lesion was primary in the cardia and in 3 in the esophagus. There were 5 deaths, the last eighteen resections being carried out without a fatality.

A new method for the construction of artificial antethoracic esophagus developed in experimental animals by Longmire and Ravitch [34] has been used in the treatment of 3 patients with benign esophageal lesions. An isolated segment of jejunum enclosed in a skin tube is transferred to the anterior wall of the chest to serve as a channel between the cervical esophagus and the stomach. The use of a free jejunal graft allows the intestine to be transplanted wherever needed, unrestricted by an

30. Boros, E.: Carcinoma of the Esophagus: A Survey of Three Hundred and Thirty-Two Cases, Gastroenterology 5:106-111, 1945.

31. Postoloff, A. V., and Cannon, W. M.: Genesis of Aortic Perforation Secondary to Carcinoma of the Esophagus, Arch. Path. 41:533-539 (May) 1946.

32. Sweet, R. H.: Surgical Management of Carcinoma of the Midthoracic Esophagus, New England J. Med. 233:1-7, 1945.

33. Clagett, O. T.: Transthoracic Resection of Lesions of the Lower Portion of the Esophagus and Cardia of the Stomach, Proc. Staff Meet., Mayo Clin. 20: 506-507, 1945.

34. Longmire, W. P., Jr., and Ravitch, M. M.: A New Method for Constructing an Artificial Esophagus, Tr. South. S. A. 57:346-362, 1946.

attached mesentery. It provides a channel completely lined with mucous membrane and possessing active peristalsis to aid in the transportation of the swallowed bolus to the stomach.

STOMACH

Anatomic Considerations.—Studies of 126 stomachs obtained at autopsy revealed ranges in weight from 77 to 453 Gm., with an average of 165 Gm. for men and 150 Gm. for women. Extreme values for the mucosal area were 520 and 1,536 sq. cm., with average values of 843 sq. cm. for men and 763 sq. cm. for women. The ages of the patients ranged from 19 to 83. The variations in the size of the stomach were not accounted for by differences in sex, age, or size of the body.[35] In a transposition of the stomach to the right, reported by Guttman and Thompson,[36] the duodenum, liver and gallbladder were on the left; the colon remained in its normal position.

Diverticula.—Resnick,[37] in a series of 1,000 consecutive examinations with barium meal, found diverticula of the fundic portion in 3 instances. Moses [38] described an instance of diverticula of the stomach and found about 150 reported in the literature. The most frequent location is on the posterior wall near the lesser curvature in the region of the cardia.

Diaphragmatic Hernia.—In an analysis by Adams and Lee,[39] diaphragmatic hernia was noted in about 2 per cent of all patients examined roentgenologically for gastrointestinal disease; in 64.7 per cent of the 34 cases found the hernia was of the esophageal type. The lesion was seen most frequently in obese patients in the fifth and sixth decades. The symptoms were related to the organ involved or displaced by the hernia. Surgical repair effected through the transpleural route was preferred in recurrent or traumatic hernia. In 34 cases the mortality rate was 3 per cent; 70 per cent (24) had no evidence of recurrence as revealed by roentgenologic study or symptoms from six months to four years postoperatively. Paralysis of the diaphragm by temporary section of the phrenic nerve was found by Vargas and Larach,[40] to be

35. Cox, A. J.: Variations in Size of the Human Stomach, California & West. Med. **63**:267-268, 1945.

36. Guttman, A. P., and Thompson, I. M.: Partial Transposition of the Upper Abdominal Viscera, Canad. M. A. J. **54**:486-487, 1946.

37. Resnick, B.: Diverticulum of the Cardia of the Stomach, Am. J. Roentgenol. **55**:730-733, 1946.

38. Moses, W. R.: Diverticula of the Stomach, Arch. Surg. **52**:59-65 (Jan.) 1946.

39. Adams, R., and Lee, W. F., Jr.: Diaphragmatic Hernia: A Clinical Report of Thirty-Four Surgically Treated Cases, S. Clin. North America **26**:742-750, 1946.

40. Vargas, M., and Larach, N. A.: Hernia diafragmática, Rev. méd. de Chile **73**:687-697, 1945

ineffective. Traumatic eventration is cured by surgical repair of the defect.[41]

In 1,000 consecutive roentgenologic examinations by Mendelsohn [42] 16 cases of hiatal hernia were observed; in 5 the symptoms were attributed to the hernia, and in 3 there was hematemesis. Venous congestion of the herniated portion of the stomach is postulated as the cause of bleeding.

In a report by Lintz [43] the patient complained of pain radiating to the left arm and clavicle. The author attributes this to interference with venous return to the heart, increased venous pressure and cardiac embarrassment. In view of the work of Jones,[44] this hypothesis is unnecessary and unproved, as is the assumption that the bleeding may be due to increased venous stasis.

Prolapsed Pyloric Mucosa.—There are two reports of prolapsed pyloric mucosa, each describing 2 cases in which the diagnosis was proved at operation. The roentgenologic evidence was suggestive, but the interpretation was not easy. Microscopic examination revealed an inflammatory reaction with monocytic infiltration.[45]

Hypertrophic Pyloric Stenosis in Infants.—Miller and Ostrum,[46] in discussing the roentgenologic differential diagnosis of hypertrophic pyloric stenosis in infants, conclude that the patients most likely to require operation have, as seen roentgenologically, an enlarged, slightly atonic stomach, a narrow pyloric canal elongated beyond 0.5 cm. and more than 50 per cent gastric retention under ideal conditions (usually 70 to 80 per cent) at the end of four hours. Roentgenologic study is of great value in the examination of infants with vomiting and clinical findings suggestive of pyloric stenosis in that it discloses the degree of stenosis and locates, with a reasonable degree of accuracy, the point of atresia or extrinsic pressure distal to the pyloric ring. The vast majority of cases do not call for emergency operative intervention. The patients

41. Hartzell, J. B.: Traumatic Segmental Eventration of the Diaphragm, U. S. Nav. M. Bull. **45**:323-327, 1945.

42. Mendelsohn, E. A.: Hiatus Hernia of the Stomach as a Source of Gastro-Intestinal Bleeding, Radiology **46**:502-506, 1946.

43. Lintz, W.: A New Conception of Diaphragmatic Hernia, M. Rec. **159**: 25-30 and 93-95, 1946.

44. Jones, C. M.: Hiatus Esophageal Hernia, New England J. Med. **225**: 963-972, 1941.

45. Norgore, M., and Shuler, I. J. D.: Extrusion of Gastric Mucosa Through the Pylorus, Surgery **18**:452-457, 1945. MacKenzie, W. C.; Macleod, J. W., and Bouchard, J. L.: Trans-Pyloric Prolapse of Redundant Gastric Mucosal Folds, Canad. M. A. J. **54**:553-558, 1946.

46. Miller, R. F., and Ostrum, H. W.: Hypertrophic Pyloric Stenosis in Infants: Roentgenological Differential Diagnosis, Am. J. Roentgenol. **54**:17-29, 1945.

requiring surgical treatment can usually be separated from those responding to medical management. Of 38 patients not subjected to operation and relieved by medical management, the condition in 18 was apparently due to an adynamic "ileus-like" state of the small intestine, considered to result largely from aerophagia. These responded readily to treatment directed to the elimination and prohibition of accumulation of gas in the small intestine. In the remaining 20, a moderate hypertrophy of the pyloric muscle may have been present with the canal not elongated beyond 0.5 cm. The symptoms were attributed largely to disturbed gastric motor function, easily controlled by feedings of thick gruel. All patients were free from symptoms two to six months after the examination.

Of 30 patients with congenital hypertrophic stenosis, 27 (90 per cent) were males; 27 were white and 3 were Negroes. The age at onset of the symptoms ranged from birth (1 case) to 3 months (27 cases). Ninety-three per cent had projectile vomiting on admission to the hospital. In all visible peristalsis was present, and all except 1 were constipated. A palpable pyloric tumor was present in 8 (26.7 per cent); a questionable tumor was present in 3 and no tumor in 19. The Rammstedt-Fredet pyloroplasty was performed in 29 of 30. Of the 29 patients surgically treated, 28 recovered. There was 1 death from generalized peritonitis.[47]

Volvulus.—Hamilton [48] discusses the various types of volvulus and abnormal rotations of the stomach. Rose [49] ascribes the condition in 1 case to a ropelike adhesion fixing the lesser curvature of the stomach to the anterior abdominal wall. The greater curvature was adherent to the transverse colon at a point diametrically opposite the first band. The stomach was dilated both proximally and distally to these adhesions, which formed an axis around which the two portions of the stomach could rotate.

GASTRIC PHYSIOLOGY

Mucosa.—Cox and Barnes [50] found an increase in the number of parietal cells in the mucosa of the guinea pig's stomach after protracted stimulation with histamine over a period of from two to four weeks. The increase was thought to represent a true hyperplasia and to provide a possible explanation of differences in the number of secreting cells in different human stomachs.

47. Conte, A. N., and McNally, J. T.: Congenital Hypertrophic Stenosis: Review of Thirty Cases, Arch. Pediat. **63**:1-7, 1946.

48. Hamilton, J. B.: Gastric Volvulus and Other Abnormal Rotations of the Stomach, Am. J. Roentgenol. **54**:30-40, 1945.

49. Rose, B. T.: Volvulus of the Stomach, Brit. J. Surg. **33**:93-94, 1945.

50. Cox, A. J., and Barnes, V. R.: Experimental Hyperplasia of the Stomach Mucosa, Proc. Soc. Exper. Biol. & Med. **60**:118-120, 1945.

Deficiency of calcium in rats resulted in gastric lesions consisting of necrosis, hemorrhage and epithelial hyperplasia. Addition of phosphate accentuated the lesions, and administration of vitamin D reduced them. Deficiency of thiamine or vitamin B complex also produced lesions of the same type. These lesions healed after the addition of calcium to the diet, but lesions due to deficiency of calcium were not prevented by administration of thiamine. The administration of neutralizing agents had no effect, indicating that peptic activity played no role.[51] Further studies disclosed that the lesions were not caused by the lack of any specific food factor.[52]

Motility.—Bozler[53] studied the action potentials of the stomach.

Meyer and others[54] found that under various conditions contractions due to hunger are not perceived by patients. This is in accord with the earlier unpublished observations of the reviewers to the effect that in untrained observers "hunger contractions" and the "hunger pang" constitute a small and often neglible portion of the hunger complex.

However, Peterson and Peterson,[55] in their studies of "dibutoline" (dibutylcarbamate of dimethylethyl-β-hydroxyethyl ammonium sulfate), found that the subcutaneous injection of 0.65 to 10 mg. produced a decrease in or a complete absence of contractions in human subjects with insulin-induced hypermotility and that attenuation or absence of the sensation of hunger ensued. The duration of the inhibited motility was less than when atropine was given. A subcutaneous dose sufficient to decrease salivary secretion and inhibit gastric motility was without cardiac effects or detectable effect on the intrinsic muscles of the eye.

Welch[56] describes the normal gastric feeding reflex as an immediate relaxation of the muscular walls of the stomach on the first taste of food. Under various conditions this reflex is distorted, with the result that instead of relaxation there is an immediate increase in tone or peristaltic activity or both. The degree of distortion is roughly propor-

51. Zucker, T. F.; Berg, B. N., and Zucker, L. M.: Nutritional Effects on the Gastric Mucosa of the Rat: I. Lesions of the Antrum, J. Nutrition **30**:301-317, 1945.

52. Zucker, T. F.; Berg, B. N., and Zucker, L. M.: Nutritional Effects on the Gastric Mucosa of the Rat: II. Lesions of the Fundus and Rumen, J. Nutrition **30**:319-331, 1945.

53. Bozler, E.: The Action Potentials of the Stomach, Am. J. Physiol. **144**:693-700, 1945.

54. Meyer, J.; Sorter, H., and Necheles, H.: Observations on Anorexia, Gastroenterology **5**:283-289, 1945.

55. Peterson, C. G., and Peterson, B. A.: Dibutoline: II. Effect on Insulin-Induced Gastric Hypermotility in Human Subjects, and Other Observations, Gastroenterology **5**:169-174, 1945.

56. Welch, P. B.: Distortions of the Gastric Feeding Reflex, J. A. M. A. **129**:204-207 (Sept. 15) 1945.

tional to the intensity of the symptoms and is invariably associated with the following characteristic group of symptoms: fulness, pressure, distress, eructations, heartburn or actual pain in the epigastrium, left upper abdominal quadrant or substernal region. These are the symptoms of functional motor disturbances of the digestive tract; however, we question the propriety of ascribing them to a distortion of the gastric feeding reflex per se.

Relaxation of the Cardia.—Berk [57] ascribes symptoms in 1 patient to relaxation of the cardia, but the evidence is not convincing, nor is that reported by Alvarez [58] as indicative of a congenital absence of the cardia with alleviation of the upper abdominal distress following a loss of 46 pounds (20.9 Kg.) of weight.

Abowitz [59] discusses diaphragmatic hernia and dilated esophageal ampulla, emphasizing the importance of the exclusion of these conditions by roentgenologic examination in patients with atypical angina pectoris.

Secretion.—The secretion of mucus has been carefully studied by Hollander and others [60] in five hundred specimens from Heidenhain pouches in 7 dogs. Mucus may be fluid or jelly-like or of any intermediate consistency; it may be transparent, translucent or completely opaque,, or it may contain all and varying combinations of cells, detritus, leukocytes and occasional erythrocytes. Increasing viscosity, opacity and columnar cell content are correlated with each other statistically. Pure mucus is colorless, transparent, of variable consistency and free of suspended material; opacity is due to suspended material, chiefly desquamated columnar cells. Certain authors have described simplified methods for the assay of pepsin.[61] Kolm, Komarov and Shay [62] studied the excretion of neutral red by the gastric glands in acute experiments on 17 dogs and 6 cats. In doses of 7.2 to 20 mg. per kilogram intravenously

57. Berk, M.: Cardio-Esophageal Relaxation, Gastroenterology **5**:290-298, 1945.

58. Alvarez, W. C.: Congenital Absence of the Cardia: A Case Report, Gastroenterology **5**:135-136, 1945.

59. Abowitz, J.: Diaphragmatic Hernia and Dilated Esophageal Ampulla: Their Clinical and Diagnostic Significance, Am. J. Roentgenol. **54**:483-486, 1945.

60. Hollander, F.; Stein, J., and Lauber, F. U.: The Consistency, Opacity, and Columnar Cell Content of Gastric Mucus Secreted Under the Influence of Several Mild Irritants, Gastroenterology **6**:576-595, 1946.

61. Kleiner, I. S.: A Simple Procedure for Determining the Approximate Concentration of Pepsin in Gastric Contents, J. Lab. & Clin. Med. **30**:634-635, 1945. Fennel, E. A.: Gastric Juice: Simple Methods for Quantitative Determinations of Protein Digestion and Pepsin Values, Am. J. Clin. Path. **10**:86-88, 1946. Bucher, G. R.; Grossman, M. I., and Ivy, A. C.: A Pepsin Method: The Role of Dilution in the Determination of Peptic Activity, Gastroenterology **5**:501-511, 1945.

62. Kolm, R.; Komarov, S. A., and Shay, H.: Experimental Studies on the Excretion of Neutral Red by the Stomach, Gastroenterology **5**:303-319, 1945.

neutral red acted as a mild gastric secretagogue. A small increase in the rate of secretion and acidity (or a decrease in the alkalinity) of the juice was noted. In most experiments pepsin was also increased. These effects, especially those relating to activity of pepsin, were prevented to a considerable degree by preliminary atropinization and to a lesser degree by double cervical vagotomy. Administration of large doses of atropine failed to abolish completely the stimulating action of the dye on the parietal cells. The dye was not excreted by the pyloric mucosa, the mucus or mucoid cells or by the peptic cells. In atropinized animals neutral red was absorbed and was stored for many hours as a yellow pigment by the parietal cells when these cells were not secreting actively and at a time when the excretion of neutral red had already reached low levels. Histamine administered three to six hours after the neutral red caused the elimination of large quantities of neutral red with the gastric juice. After the administration of histamine, the increase in the concentration of neutral red paralleled the acidity and the concentration of pepsin. As the secretion of histamine continued there was a diminution in the concentration of neutral red excreted with the juice. This was paralleled by a decrease in pepsin even if the acidity and the rate of secretion continued to rise. The process was interpreted as a manifestation of the "washing out" effect described by Babkin.

In rats on a diet deficient in thiamine but with other vitamin B factors included the volume of spontaneous gastric secretion was much greater than it was in controls, while the acidity, peptic power and total concentration of chlorides remained normal. Gastric ulceration, more frequent and severe in rats with thiamine-depleted diets than in those with calorically restricted but thiamine-adequate diets, was attributed by Shay and others [63] to the increased gastric secretion.

Rehm and Evelow [64] have shown that in dogs given histamine as a stimulus the injection of sodium thiocyanate (4.1 Gm.) causes a decrease in the magnitude of the gastric potential, approaching that of the resting stomach. Thus administration of sodium thiocyanate in appropriate amounts results in complete inhibition of secretion of histamine and an increase of the potential difference across the stomach at the resting level. The use of thiocyanate in comparable amounts has no effect on the potential of the resting stomach.

Hartiala and Karvonen [65] conclude that the decrease of acid secretion during severe deficiency of oxygen is a consequence of anoxia and independent of the alkalosis.

63. Shay, H.; Komarov, S. A.; Gruenstein, M., and Fels, S. S.: The Effect of Thiamin Deprivation upon Gastric Secretion in Rats, Gastroenterology 6:199-212, 1946.

64. Rehm, W. S., and Evelow, A. J.: The Effect of Thiocyanate on Gastric Potential and Secretion, Am. J. Physiol. 144:701-705, 1945.

65. Hartiala, K., and Karvonen, M.: The Influence of Anoxia on the Gastric HCl-Secretion, Acta physiol. Scandinav. 11:85-96, 1946.

The synthetic histamine antagonists, B-dimethylaminoethyl benzhydryl ether hydrochloride and N'pyridyl-N'benzyl N/dimethylethylenediamine, in doses of 50 mg. subcutaneously do not significantly reduce the response of the gastric glands of dogs to stimulation by histamine administered subcutaneously every ten minutes,[66] although a certain degree of inhibition as judged by the response to the alcohol test meal was noted in human subjects.[67]

Bilateral vagotomy in cats and administration of 1 mg. of atropine sulfate in human beings or cats does not abolish the response to caffeine. Caffeine, like histamine, predominantly acts peripherally on the glandular mechanism. The output and concentration of pepsin are increased to a greater extent by caffeine than by histamine in human beings, according to Roth and Ivy.[68] In human beings and cats caffeine stimulates gastric secretion by direct glandular action, whereas in dogs this effect does not occur. McCarthy [69] has shown that a definite lowering of the secretion of acid, frequently with complete anacidity, follows double vagotomy and partial gastrectomy in dogs.

Urogastrone prepared from normal dogs inhibits gastric secretion in the majority of experiments after injection of histamine (inhibition in 63 per cent, augmentation in 18.5 per cent and no change in 18.5 per cent). Urogastrone prepared from thyroidectomized and oophorectomized dogs inhibits gastric secretion in approximately the same percentage of the experiments as the urogastrone prepared from the normal dogs. Extracts prepared from oophorectomized dogs apparently contain less urogastrone. Extracts prepared from 2 hypophysectomized animals inhibited gastric secretion in only five of fifty-two studies (9.5 per cent); in thirty-two of fifty-two observations (61.5 per cent) a significant increase in the quantity of secretion was noted, the augmentation sometimes reaching 200 per cent. Thus Sandweiss and his co-workers [70] conclude that the inhibitory factor in urogastrone may be of hypophysial origin.

66. Sangster, W.; Grossman, M., and Ivy, A. C.: The Effect of Two New Histamine Antagonists (Benadryl and Compound 63) on Histamine Stimulated Gastric Secretion in the Dog, Gastroenterology 6:436-438, 1946.

67. McGavack, T. H.; Elias, H., and Boyd, L. J.: The Influence of Benadryl (Dimethylaminoethyl-Benzhydryl Ether Hydrochloride) on Gastric Acidity, Gastroenterology 6:439-442, 1946.

68. Roth, J. A., and Ivy, A. C.: The Effect of Vagotomy and Atropine upon Caffeine Stimulation of Gastric Secretion, Gastroenterology 5:129-134, 1945.

69. McCarthy, H. H.: The Effect of Vagotomy and Partial Gastrectomy on Gastric Acidity: Effect of Stimulation of the Psychic Phase in the Presence of Tenth Normal Hydrochloric Acid in the Stomach, Proc. Staff Meet., Mayo Clin. 21:142-150, 1946.

70. Kaulbersz, J.; Patterson, T. L.; Sandweiss, D. J., and Saltzstein, H. G.: The Relation of Endocrine Glands to Gastric Secretory Depressant in Urine (Urogastrone), Science 102:530-531, 1945.

Friedman and Sandweiss [71] describe a method for the bio-assay of extracts inhibiting gastric secretion.

Wolman [72] found that in children the fasting secretion exhibits wide normal ranges in volume, rate of formation, p_H, pepsin content and acidity. Pepsin and hydrochloric acid seem to be secreted in more or less parallel fashion. The buffer capacity of a glass of cow's milk is relatively so great that fasting specimens richest in free hydrochloric acid will become almost completely neutralized.

Glenn, [73] in a comparison of 200 soldiers with duodenal ulcer and 250 control patients with functional digestive disturbances, found little difference in the histamine secretion in terms of the peak of free and total acidity. However, when the total volume and the total acid secretion are calculated, there is a greater difference in the two groups, tending to support the theory of hypersecretion in duodenal ulcer. No significant secretory abnormality was observed in 25 patients with rheumatoid arthritis. [74]

GASTROSCOPY

There have been a number of studies of the correlation between gastroscopy and roentgen examination in the demonstration of gastric disease. Benedict [75] in a series of 245 cases found that roentgenologic examination and gastroscopy were of about equal value in 54 per cent of the cases, and roentgenologic examination was considered superior in 29 per cent and gastroscopy superior in 17 per cent. Ricketts and Pollard [76] in an analysis of 1,297 patients found 355 with conflicting gastroscopic and roentgenologic findings. Gastroscopy failed to reveal the lesions seen by roentgenologic study in 46 cases, including 22 cases of benign ulcer, 21 of carcinoma, 2 of benign polyposis and 1 of gastric diverticulum. Conversely, gastroscopy revealed disease, while roentgenograms showed normal condition in 309, including 269 cases of chronic gastritis, 26 cases of benign ulcer, 10 cases of carcinoma and 4 cases of polyps. Monat and Thompson [77] made a similar study of 500

71. Friedman, M. H. F., and Sandweiss, D. J.: A Method for Bio-Assay for Extracts Which Inhibit Gastric Secretion, Am. J. Digest. Dis. **13**:108-109, 1946.

72. Wolman, I. J.: Gastric Phase of Milk Digestion in Childhood, Am. J. Dis. Child. **71**:394-422 (April) 1946.

73. Glenn, P. M.: Histamine Stimulated Fractional Gastric Analysis: The Diagnostic Value of Total Secretion, Gastroenterology **6**:409-416, 1946.

74. Lucchesi, O., and Lucchesi, M.: Gastric Acidity in Rheumatoid Arthritis, Gastroenterology **5**:299-302, 1945.

75. Benedict, E. B.: Correlation of Gastroscopic, Roentgenologic and Pathologic Findings in Diseases of the Stomach: An Analysis of Two Hundred and Forty-Five Proved Cases, Am. J. Roentgenol. **55**:251-274, 1946.

76. Ricketts, W. E., and Pollard, H. M.: A Roentgenologic and Gastroscopic Study of Gastric Disease, Gastroenterology **6**:1-6, 1946.

77. Monat, H. A., and Thompson, C. M.: Evaluation of Gastroscopic, Roentgen, Sigmoidoscopic and Laboratory Procedures in Five Hundred Gastrointestinal Cases, Rev. Gastroenterol. **13**:19-23, 1946.

patients in a naval hospital. Johnson[78] further discusses the clinical value of gastroscopy. Barowsky[79] comments particularly on the differentiation of benign and malignant ulcers and gives the distinguishing features.

Two instances are reported of apparent rupture of the stomach during gastroscopy, with pneumoperitoneum present at operation but no demonstrable lesion.[80] Two fatal hypopharyngeal perforations of the esophagus with the flexible gastroscope are described by Fletcher and Jones,[81] who consider this to be the most serious risk of gastroscopy and not so infrequent as the rarity of reported cases suggests. We question this statement, for since the case described by Schindler[82] in 1940 in 22,351 gastroscopies only 1 similar instance has come to our attention.

Kenamore and his associates[83] describe a forceps for use in biopsy with the gastroscope and the results of its application in 35 cases. There were no untoward reactions, but in some instances attempts to remove tissue were unsuccessful.

GASTRITIS

Maimon and Palmer[84] discuss the significance of chronic gastritis on the basis of 14 patients observed gastroscopically for periods varying from eight months to eleven years. Superficial and hypertrophic gastritis appear to be variations of the same process rather than distinct and separate entities. The prognostic implications of both the moderate and severe grades are not significantly different, both tending to prolonged chronicity. Atrophic gastritis without admixtures of the hypertrophic or superficial forms was observed to be constant for periods up to five years. In some instances the atrophic gastritis did seem to appear as a sequela of hypertrophic and superficial gastritis. Atrophic gastritis when severe tends to persist, but return to normal has been observed. No detectable serious consequences were observed in patients with gastritis

78. Johnson, T. A.: Clinical Value of Gastroscopy, M. Clin. North America **30**:303-306, 1946.

79. Barowsky, H.: Gastroscopy, Rev. Gastroenterol. **13**:104-117, 1946.

80. Schindler, R.: Passage of Air Through the Gastric Wall During Gastroscopy, with No Wound Demonstrable Three Hours Later, Gastroenterology **5**:34-36, 1945. Berk, J. E.: Pneumoperitoneum Following Gastroscopy Without Evidence of Perforation at Laparotomy Fourteen Hours Later, ibid. **6**:218, 1946.

81. Fletcher, C. M., and Jones, F. A.: The Risks of Gastroscopy with the Flexible Gastroscope, Brit. M. J. **2**:421-422, 1945.

82. Schindler, R.: Results of the Questionnaire on Fatalities in Gastroscopy, Am. J. Digest. Dis. **7**:293-295, 1940.

83. Kenamore, B.; Scheff, H., and Womack, N. A.: Study of Gastric Lesions by Means of Biopsy Specimens Removed Endoscopically, Arch. Surg. **52**:50-58 (Jan.) 1946.

84. Maimon, S. N., and Palmer, W. L.: Chronic Gastritis: Observations on Its Course and Significance, Gastroenterology **6**:511-536, 1946.

of up to eleven years' duration. The symptoms could not be correlated with the appearance of the gastric mucosa. Inconstant changes were noted after roentgen therapy in 6 patients; previously observed hypertrophic changes were not found after vagotomy in 2 patients. The clinical significance of chronic gastritis is considered as still unproved.

Cutler and Walther,[85] in studying the significance of chronic gastritis, divided 333 soldiers into three groups: Group A comprised 33 asymptomatic volunteers; 30 (91 per cent) were normal, and 3 were considered gastroscopically to have atrophic gastritis. In group B, consisting of 36 patients with duodenal ulcer, atrophic, superficial or combined superficial and atrophic changes were present in 52 per cent; single erosions were noted in 2 others. In group C, comprising 264 patients with distress in the upper abdominal area and normal roentgenograms of the gastroduodenum, 52 per cent were normal, and 40 per cent had gastritis, classified as follows: 19 per cent superficial, 12 per cent atrophic, 2 per cent hypertrophic and 7 per cent combined superficial and atrophic. Three per cent (of 264) had mucosal erosions and 5 per cent mucosal hemorrhages. No uniform symptom complex was demonstrated except that in the hypertrophic group the distress resembled that of peptic ulcer.

The mucosa has been studied gastroscopically in a variety of conditions. Freeman[86] noted hyperplasia in 76 per cent of 50 patients with duodenal ulcer and hence is inclined to correlate hyperplasia with an increased secretion of acid gastric juice. In 10 patients with infectious hepatitis superficial gastritis was noted in 1; the others were normal.[87] In 20 patients examined three to four weeks after a staphylococcic food poisoning no correlation was noted between the gastroscopic findings and the symptoms.[88] Studies of 22 patients with chronic seasickness disclosed nothing unusual.[89] In 20 patients with nausea and vomiting from salicylism no significant changes were noted.[90]

Arendt[91] emphasizes again the problem of the differentiation of chronic hypertrophic antral gastritis from carcinoma. In a patient seen

85. Cutler, J. G., and Walther, J. E.: The Significance of Chronic Gastritis in an Army General Hospital, Gastroenterology 5:112-116, 1945.

86. Freeman, H.: Duodenal Ulceration: A Gastroscopic Study of the Gastric Mucosa and Its Surgical Significance, Brit. M. J. 1:980-982, 1946.

87. Monat, H. A.; Robins, A. L., and Glanz, S.: Gastric Mucosa in Infectious Hepatitis: Roentgenologic and Gastroscopic Studies; Report on Ten Cases, Rev. Gastroenterol. 13:102-104, 1946.

88. Schwartz, I. R.: A Gastroscopic Study Following an Outbreak of Food Poisoning, Gastroenterology 6:105-111, 1946.

89. Benedict, E. B., and Schwab, R. S.: Gastroscopic Studies in Naval Personnel with Chronic Seasickness, New England J. Med. 233:237, 1945.

90. Caravati, C. M.: Gastric Endoscopic and Secretory Findings During Salicylism, Gastroenterology 6:7-8, 1946.

91. Arendt, J.: Chronic Hypertrophic Antrum Gastritis, Ann. Surg. 122:235-252, 1945.

by Ortmayer and others [92] for whom a clinical diagnosis of carcinoma was made, histologic examination revealed a subacute to chronic granulomatous ulcerative gastritis of unknown cause.

Weens [93] reports the rare instance of a patient in whom an emphysematous inflammation of the stomach developed after ingestion of concentrated hydrochloric acid. Extensive formation of gas in the gastric wall was demonstrated roentgenologically for a period of approximately four weeks. The infection of the stomach was followed by notable scar formation, which resulted in a complete obstruction of the mid-portion of the stomach and necessitated two gastrostomies. Culture of the blood revealed Aerobacter aerogenes; Proteus vulgaris was cultured from the gastric contents. After temporary recovery for three months a subphrenic abscess developed, followed by fatal thrombosis of the splenic and gastroepiploic veins and multiple abscesses of the liver.

TUBERCULOSIS

Windwer [94] reports an instance of tuberculosis of the stomach, the only one recorded among 21,000 patients admitted in thirty-one years to a metropolitan hospital; it was diagnosed by the pathologist after microscopic study of the tissue including the lymph nodes. Subsequently, there developed ulcerative colitis, fistula in ano and a rectal granuloma, which on histopathologic study was shown to contain tubercle bacilli. At no time was there evidence of pulmonary involvement. Binder and others [95] review 61 cases of gastric tuberculosis in children 15 years or younger compiled from the literature. The ratio of the incidence of the lesion in adults and in children is 5 to 1. Ulcers are present in 95 per cent of the cases, the lower two thirds of the stomach being involved more frequently than the cardia. Vomiting, emaciation and diarrhea are the most frequent symptoms.

HEMATEMESIS

In 685 cases of severe hemorrhage of the upper part of the gastrointestinal tract seen at the Boston City Hospital the cause was not determined in 60 instances (about 9 per cent). The histories and physical conditions in this group were varied and difficult to evaluate.

92. Ortmayer, M.; Balkin, R., and Humphreys, E.: Chronic Erosive, Granulomatous, Atrophic Gastritis, Gastroenterology **6**:298-301, 1946.

93. Weens, H. S.: Emphysematous Gastritis, Am. J. Roentgenol. **55**:588-593, 1946.

94. Windwer, C.: Tuberculosis of the Stomach, Rev. Gastroenterol. **13**:38-41, 1946.

95. Binder, I.; Ruby, V. M., and Shuman, B. J.: Tuberculosis of the Stomach with Special Reference to Its Incidence in Children, Gastroenterology **5**:474-490, 1945.

Seven of the 60 patients died from the hemorrhage; autopsies were performed on 3; but the source of the bleeding was not found.[96] Gambill [97] describes a recurring hemorrhage due to hereditary telangiectasis and reviews the literature on the subject.

Reporting a study of 25 patients consecutively admitted to the hospital for massive hemorrhage, Green [98] described the immediate application of specific diagnostic procedures. The history and physical condition were often misleading and of limited value in diagnosis. After initial treatment for shock and aspiration of the stomach, roentgen examination of the upper part of the gastrointestinal tract was performed in 18 of 22 cases. The procedure was diagnostic in 16, doubtful in 1 and noncontributory in another. In no instance was harm to the patient observed. Peritoneoscopy was of positive diagnostic value in 6 of 10 cases; it helped to detect the presence of cirrhosis of the liver in 2 cases with esophageal varices and of diaphragmatic herniation in 2 cases. Roentgenograms after a barium enema, in 4 cases, did not reveal the cause of the hemorrhage. Age was found to be the most important prognostic criterion, the prognosis being excellent for patients under 45 and progressively worse for older patients. To combat shock, Green advocates the use of position, oxygen therapy, medication with barbiturates and atropine and transfusions to maintain a red blood cell count of 3,500,000. On the basis of recent papers by Drew, Dripps, Comroe and Gelfan, the use of morphine is opposed. In patients over 45 with hemorrhage from peptic ulcer immediate surgical intervention (before forty-eight hours) is favored. Patients with diaphragmatic hernia and esophageal varices should be maintained in a sitting position as soon as they are reasonably free of shock. The immediate feeding of a high caloric liquid diet composed of protein digests in milk is favored because of its neutralizing effect, the prevention of hunger contractions and the corrective influence on hypoproteinemia. The causes of hemorrhage were: peptic ulcer in 11 cases; esophageal varices in 6, diaphragmatic hernia in 3, mesenteric thrombosis in 1, ileitis in 1 and gastritis in 1; in 2 the cause was questionable. Fifteen patients were treated medically throughout, with one fatality due to thrombosis of the mesenteric artery. Of 7 treated surgically, 1 died on the sixth day from atelectasis and pneumonia.

96. Jankelson, I. R.: Massive Hematemesis of Undetermined Origin, Gastroenterology 5:96-101, 1945.

97. Gambill, E. E.: Recurring Gastro-Intestinal Hemorrhage in Hereditary Hemorrhagic Telangiectasia: Incidence and Report of a Case, Proc. Staff Meet., Mayo Clin. 21:157-160, 1946.

98. Green, D. M.: The Medical Approach to Massive Gastro-Intestinal Hemorrhage, Northwest Med. 45:325-332, 1946.

Greenblatt and Cohn [99] studied the azotemia of hemorrhage experimentally by bleeding normal adults and then feeding them the blood withdrawn. There seems to be a critical level, somewhere between 580 cc. and 800 cc. of whole blood, at which blood lost from the vascular system and artificially "bled" into the intestinal tract produces no significant azotemia; with larger amounts azotemia occurs. The observations support the contention of Block and of Johnson that the azotemia of hemorrhage is due primarily to a loss of fluid sufficient to impair normal renal function; the absorption of nitrogenous compounds is an additional factor.

PEPTIC ULCER

Incidence.—There were 43,000 deaths in England and Wales in the ten years before the war as the result of peptic ulceration. In two years 23,574 men were discharged from the army (British) with this condition. It is estimated that 200,000 fresh instances occur in England and Wales alone each year involving males.[100]

Experimental Work.—Shay and others [101] describe a simple method for the uniform production of gastric ulceration in the rat. It consists in ligation of the pylorus and killing of the animals seventeen to nineteen hours later. The procedure is suggested as a method for assaying antiulcer hormones.

Total thyroidectomy was found by Wu [102] to have no influence on the formation of Mann-Williamson ulcers.

In an extensive study of peptic activity Driver [103] found that pepsin in tenth-normal sodium bicarbonate will not produce ulcers in the small intestine of the dog, with or without pressure. Pancreatin will do so only under a hydrostatic pressure of 90 cm. of water in ten hours. Bile salts inhibit markedly the digestive action of pepsin at a p_H of 1.25. At a p_H of 3.7 there is no damage of the mucosa regardless of the hydrostatic pressure or the presence of bile salts.[104] The digestive action of an acid-pepsin solution is reduced by lowering the tempera-

99. Greenblatt, I. J., and Cohn, T. D.: Azotemia in Gastro-Intestinal Bleeding: The Ingestion of Shed Blood in Humans, Am. J. M. Sc. **211:**565-570, 1946.

100. Wood, W. Q.: The Treatment of Duodenal Ulcer, Edinburgh M. J. **52:** 433-450, 1945.

101. Shay, H.; Komarov, S. A.; Fels, S. S.; Meranze, D.; Gruenstein, M., and Siplet, H.: A Simple Method for the Uniform Production of Gastric Ulceration in the Rat, Gastroenterology **5:**43-61, 1945.

102. Wu, P. P. T.: Effect of Total Thyroidectomy on Experimental Production of Peptic Ulcer, Surgery **18:**619-623, 1945.

103. Driver, R. L.: Comparative Efficacy of Pancreatin and Pepsin in the Experimental Production of Intestinal Ulcers, Arch. Path. **40:**34-36 (July) 1945.

104. Driver, R. L., and Carmichael, E. B.: The Effect of Bile Salts on the Experimental Production of Ulcers in the Dog, Am. J. Digest. Dis. **12:**378-379, 1945.

ture.[105] The action of mineral oil markedly inhibits the digestive action.[106]

Freeman and Li[107] observed that the incidence of peptic ulcer among 32 dogs fed a diet deficient in protein was 47 per cent at the time of death. The lowering of the dietary fat and the addition of bile salts seemed to favor the formation of ulcers in animals deficient in protein. The incidence could not be correlated with the survival period, hepatic dye, clearance, serum phosphatase activity or lipid content of the liver.

Hartman's observations[108] in experimental Curling's ulcers are of interest. Of 28 control dogs given third degree burns involving over 50 to 60 per cent of the shaved body surface, blood cultures were obtained in all; in 77.7 per cent acute duodenal ulcers developed. In 10 dogs similarly burned, but given penicillin intramuscularly in amounts ranging from 10,000 to 50,000 units daily, acute ulcers developed in only 23 per cent. This observation is interpreted as suggesting that systemic infection may be of major etiologic importance in the total pathogenesis of acute duodenal ulcers. Pathologic studies, however, demonstrated that the final stage of ulceration was a corrosive process and not a local infection. The number of animals used was small; the results are not sufficient to convince us that infection played a significant role.

Two investigators report interesting observations on ulcers produced by cinchophen. In 10 dogs fed yellow cinchophen peptic ulceration developed, whereas in 12 other dogs fed in exactly the same way, with the addition of a preparation from the mucosa and submucosa of a hog's stomach and duodenum, no ulcerations were found. Morrison[109] suggests that "a protective principle" is elaborated by the gastric mucosa to enable it to resist self digestion and formation of ulcer. Nasio[110] reports that the parenteral administration of 5 mg. of calciferol (vitamin D_2) daily prevented the development of cinchophen ulcers in 60 per cent of 12 dogs. Parenteral administration of ascorbic acid had a similar effect, whereas the following vitamins were of no value: thiamine, given orally and parenterally; riboflavin, given parenterally;

105. Driver, R. L.: Effect of Temperature on the Experimental Production of Ulcers in the Intestines of Dogs, Am. J. Digest. Dis. **12**:394-395, 1945.

106. Driver, R. L.: The Inhibitory Effect of Mineral Oil on the Experimental Production of Ulcers, Am. J. Digest. Dis. **12**:395-396, 1945.

107. Li, T. W., and Freeman, S.: The Frequency of "Peptic" Ulcers in Protein-Deficient Dogs, Gastroenterology **6**:140-144, 1946.

108. Hartman, F. W.: Curling's Ulcer in Experimental Burns: II. The Effect of Penicillin Therapy, Gastroenterology **6**:130-139, 1946.

109. Morrison, L. M.: II. The Prevention of Induced Peptic Ulcer in Dogs by Feeding a Hog Stomach Preparation, Am. J. Digest. Dis. **12**:328-330, 1945.

110. Nasio, J.: Action of Vitamin D_2 on Experimental Peptic Ulcer Produced by Cinchophen, Gastroenterology **5**:496-500, 1945.

and vitamin K, given parenterally. Parenteral administration of both nicotinic acid and nicotinamide seemed to hasten the development of ulcer. Parenteral administration of diethylstilbestrol prevented the development of ulcers in 100 per cent of the male dogs and in 22 per cent of the female dogs given cinchophen. Parenterally administered estriol prevented their development in 60 per cent of the animals, but large lesions developed in the others. The administration of chorionic gonadotropin prevented ulcers in 40 per cent of the animals, and the use of "synapoidin" (mixture of chorionic gonadotropin and follicle-stimulating hormone from anterior pituitary glands) prevented and cured ulcers in 65 per cent.[111] We find the positive results obtained by Morrison and Nasio difficult to understand. The experiments with the hog's gastric mucosa, diethylstilbestrol, estriol, and chorionic gonadotropin are all of great interest; they should be repeated and, if confirmed, extended.

Giddings, Wynn and Haldi [112] have restudied the experimental production of ulcer with caffeine. The administration of 75 mg. of caffeine per kilogram of body weight by stomach tube to 26 cats daily for twenty-one days did not produce ulcers or erosions. Injection of the same amount of caffeine daily intramuscularly in a mixture of beeswax and oil for the same length of time likewise failed to produce erosions or ulcers. Ulcers were produced by caffeine only when the dose was large enough to kill the animals. In 34 albino cats given 75 mg. of caffeine per kilogram of body weight by stomach tube over a period of eight to twenty weeks, microscopic changes compatible with erosion or ulcer developed in 3. The authors conclude that the data available offer no valid basis for the deduction that caffeine-containing beverages (as coffee or tea) play a part in the pathogenesis of ulcer in human beings.

Wangensteen [113] reviews completely the modern concepts of the causation of peptic ulcer, arriving at the following conclusions: 1. The ease of production of perforating ulcer in most laboratory animals by the implantation of histamine in beeswax emphasizes the great importance of the digestive activity of the gastric juice. 2. It is obvious that fat embolism following fracture of long bones may plug the end vessels of the mucosa to produce erosions or ulcer, which in the presence of

111. Nasio, J.: Influence of Some Vitamins and Hormones in the Prevention of Experimental Cinchophen Peptic Ulcer, Rev. Gastroenterol. **13**:195-204, 1946.

112. Giddings, G.; Wynn, W., and Haldi, J.: A Study of the Alleged Role of Caffeine in the Pathogenesis of Gastric Ulcer, Gastroenterology 5:210-217, 1945.

113. Wangensteen, O. H.: The Ulcer Problem: I. Etiology, with Special Reference to an Inter-Relationship Between the Vascular and the Acid-Peptic Digestive Factors; II. Characterization of a Satisfactory Operation Which Will Protect Against Recurrent Ulcer, Canad. M. A. J. **53**:309-331, 1945.

active gastric secretion may result in bleeding. This occurrence has been observed clinically, and its counterpart has been produced experimentally. 3. The production of severe bleeding from erosions or ulcer attending the administration of vasospastic agents such as epinephrine or betahypophamine accompanied with histamine in beeswax definitely suggests the important role of ischemia resulting from an overactive vasomotor influence when attended by active gastric secretion. 4. Partial obstruction to the venous outflow from the stomach increases the weight of the stomach, traceable to resultant edema of the gastric wall, especially of the submucosa. Such venous obstruction abets the ulcer diathesis. Bleeding erosions or ulcers may be produced by such obstructions. 5. The histamine in beeswax technic has proved a useful instrument for the appraisal of operations for ulcer It would appear that a three quarter resection carried out on the Billroth II plan, a short afferent duodenal loop being employed in which the antral mucosa and the lesser curvature of the stomach are excised, meets the requirements of a satisfactory operation for ulcer. Wangensteen's experience with this procedure in patients as well as in dogs receiving histamine suggests that intractable ulcer may be a myth.

Vagotomy failed to protect animals from the peptic ulcers induced by injections of histamine in beeswax, according to Baronofsky, Friesen, Sanchez-Palomera, Cole and Wangensteen.[114] Supradiaphragmatic section was performed on 13 dogs, 2 cats and 9 rabbits and infradiaphragmatic section on 4 cats and 5 rabbits. In 4 of the dogs gastrojejunostomy was done previously. After an interval of seven to nine days, injections of histamine in beeswax were instituted. The previous operative procedures did not protect against ulcer or erosion. The authors point out that since histamine acts directly on the parietal cell the results are not surprising and are not to be interpreted as a criticism of the application of vagotomy to the problem of ulcer in man.

Baronofsky and Wangensteen [115] have also demonstrated that the administration of nitroglycerine in beeswax aids and abets the formation of the histamine-induced ulcer. The effect of nitroglycerine is attributed to its venous pooling property, which, coupled with normal arteriolar reflex contractile responses, leads, after prolonged administration, to resultant areas of impaired circulation in the mucous membrane of the esophagus, stomach and duodenum. The resistance of these areas to acid-peptic digestion is thus lowered and ulcer results.

114. Baronofsky, I. D.; Friesen, S.; Sanchez-Palomera, E.; Cole, F., and Wangensteen, O. H.: Vagotomy Fails to Protect Against Histamine-Provoked Ulcer, Proc. Soc. Exper. Biol. & Med. **62:**114-118, 1946.

115. Baronofsky, I. D., and Wangensteen, O. H.: Role of Nitroglycerin in Accelerating Occurrence of the Histamine-Provoked Ulcer, Proc. Soc. Exper. Biol. & Med. **62:**127-129, 1946.

Grossman, Dutton and Ivy [116] studied the effect of enterogastrone on the induction of ulcers with histamine. In 5 dogs who received 100 mg. of enterogastrone concentrate daily by subcutaneous injection for thirty days prior to the initiation of daily injections of 0.5 cc. of histamine suspension and then received enterogastrone concentrate concurrent with the histamine the occurrence of peptic ulcer was not prevented. Five other dogs who received no pretreatment were given histamine and enterogastrone extract concurrently, with similar results. Enterogastrone had been found previously to have an inhibitory effect on the Mann-Williamson ulcer. Thus the factors concerned in the production of histamine-induced ulcers and Mann-Williamson ulcers seem to be different. We find this difficult to understand and suggest that further studies are needed. The discussion by Bachrach, Grossman and Ivy[117] of the resistance of the mucosa to digestion is excellent. The stomach apparently does not digest itself when the circulation of its mucosa is adequate, when the tolerance of cells to acid pepsin is not exceeded and when the nutritional or metabolic condition of the subject is adequate for the regeneration and proliferation of the cells of the mucosa and for mucus secretion. There is a gradient in the susceptibility of the mucosa to injury; the farther it is removed from the site of formation of acid pepsin the greater is the susceptibility to damage.

Iams and Horton [118] report the appearance of a gastric ulcer in a patient with multiple sclerosis under treatment with histamine. When the administration of histamine was stopped, the ulcer healed in twelve days. This is the first case in which ulcer has been encountered in the administration of more than thirty-eight thousand intravenous injections in six years, although similar cases were reported by Browne and McHardy.[119]

In conclusion of this section, we wish to call attention to the fact that there is now practically no tendency to deny the preeminent role of peptic digestion in the causation of ulcer; the lesion is in fact a "peptic ulcer." The experimental work for the past quarter of a century has slowly but surely led to this conclusion, reached by clinicians in earlier years. The oft repeated statement that nothing is known about the cause of peptic ulcer should be discarded; it is

116. Grossman, M. I.; Dutton, D. F., and Ivy, A. C.: An Attempt to Prevent Histamine-Induced Ulcers in Dogs by the Administration of Enterogastrone Concentrates, Gastroenterology **6**:145-150, 1946.

117. Bachrach, W. H.; Grossman, M. I., and Ivy, A. C.: Problems in the Etiology of Peptic Ulcer: The Resistance of the Gastrointestinal Tract to the Digestive Action of Its Own Secretions, Gastroenterology **6**:563-573, 1946.

118. Iams, A. M., and Horton, B. T.: An Ulcer Which Appeared in the Stomach of a Man Receiving Histamine Intravenously, Gastroenterology **6**:449-451, 1946.

119. McHardy, G., and Browne, D. C.: Duodenal Ulcer Developing in Man Following "Histamine Desensitization," Gastroenterology **2**:345-347, 1944.

absurd. The dictum of Schwarz, "no acid—no acid,"·has been thoroughly proved even though all phases of the process of formation of ulcer are not yet understood. .

Heredity.—The occurrence of peptic ulcer, one duodenal and one gastric, is reported by Riecker [120] in identical female twins whose father also had a peptic ulcer (duodenal). This is the fourth such instance reported in the current literature and is thought to confirm the hereditary nature of the disease. However, coincidence would seem to account for such occasional situations.

Gastric Secretion in Peptic Ulcer.—Page [121] found no significant difference in the fasting free acidity in 137 patients with roentgenologic evidence of peptic ulcer of the duodenum and 109 controls. The degree of free acidity after a fractional alcohol test meal was not significantly different in the two groups. However, while 5.5 per cent of those in the group without ulcers had a constant anacidity after administration of histamine, this did not occur in any patient in the group with ulcers.

Sandweiss and others [122] report studies of the nocturnal secretion both in normal subjects and in patients with duodenal ulcer. Following a well balanced meal at 6 p.m. (which included beef broth and fish) the nocturnal gastric juice was of the same hydrochloric acid concentration and volume in patients with ulcer as in normal subjects of the same age and sex. Only 1 out of 22 patients with ulcer were interpreted as having a tendency to hypersecretion. This report conflicts with the previous reports of other workers. Further observations under better standardized conditions will be required to determine the secretory differences between patients with peptic ulcer and control subjects. We venture to predict that an inconstant tendency to hypersecretion will be found in patients with duodenal ulcer. In our experience, a few patients with duodenal ulcer and many with gastric ulcer may be classified as "low grade secretors," although all of them do secrete acid gastric juice in response to stimulation with histamine.

Psychosomatic Aspects.—The emotional components of illness are receiving increasing attention. Mittelmann and his associates [123] carried out psychiatric interviews with 450 patients admitted to the medical and

120. Riecker, H. H.: Peptic Ulcer in Identical Twins, Ann. Int. Med. **24:** 878-882, 1946.

121. Page, R. C.: Gastric Acidity and Occult Blood Studies of Young Adult Males with Duodenal Ulcer, Rev. Gastroenterol. **12:**343-347, 1945. ·

122. Sandweiss, D. J.; Sugarman, M. H.; Podolsky, H. M., and Friedman, M. H. F.: Nocturnal Gastric Secretion in Duodenal Ulcer, J. A. M. A. **130:**258-265 (Feb. 2) 1946. .

123. Mittelmann, B.; Weider, A.; Brodman, K.; Wechsler, D., and Wolff, H. G.: Personality and Psychosomatic Disturbances in Patients on Medical and Surgical Wards: A Survey of Four Hundred and Fifty Admissions, Psychosom. Med. **7:**220-223, 1945. .

surgical wards; 20 per cent had mild neuroses and 10 per cent severe neuroses. Anxiety states with predominant gastrointestinal symptoms were present in 19 patients, readily discernible psychopathologic conditions were noted in 10 patients with peptic ulcer and 1 patient had a similar psychic disturbance with "colitis." Three patients with milder psychosomatic disturbances had peptic ulcer and another "colitis."

Psychiatric studies of 100 patients with peptic ulcer in a general hospital in the Mediterranean Theater led Halsted and Weinberg[124] to the conclusion that the personality pattern of patients with peptic ulcer is markedly different from that of the large majority of patients with psychogenic dyspepsia. Though superficial from the psychiatric viewpoint, these investigations probed the family, educational, occupational, social, marital and military background of each patient. Similar studies were made of 100 patients with chronic nonulcerative dyspepsia. The patients without ulcers were anxious to describe symptoms in detail; their symptomatology seemed to be an expression of anxiety and insecurity. On the other hand, the patients with ulcers were noncommittal and unconcerned for themselves, except for the single symptom of pain, unless direct questions were put to them. Halsted and Weinberg agree with previous workers in picturing the patient with peptic ulcer as unrelaxed, hard-driving and overaggressive. Both the patient with ulcerative and the patient with nonulcerative dyspepsia possess an underlying insecurity. The type with ulcers finds solution in an abnormal drive, restlessness and impatience; the dyspeptic type magnifies his every illness and is overcome by it.

We are sympathetic to all studies of the psychiatric factors in disease of all kinds. However, in so far as peptic ulcer is concerned, the picture does not seem complete. The tendency has been to study, report and emphasize the patients with more or less obvious emotional difficulties. Alexander described a pattern; subsequent workers have fitted their patients into this pattern. There are many persons with peptic ulcer who can scarcely be described as "unrelaxed, hard-driving and overaggressive." Bearing in mind the difficulty in defining the normal personality, we are nevertheless not convinced that the patient with peptic ulcer differs essentially from the "normal," or that the role of emotional components in the formation of peptic ulcer or in its recurrence has as yet been accurately assayed.

Pancreatic Rests and Peptic Ulcer.—The literature on pancreatic heterotopia is reviewed in two papers, and additional cases are reported.[125]

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124. Halsted, J. A., and Weinberg, H.: Peptic Ulcer Among Soldiers in the Mediterranean Theater of Operations, New England J. Med. **234**:313-320, 1946.

125. Barbosa, J. J. de C.; Dockerty, M. B., and Waugh, J. M.: Pancreatic Heterotopia: Surgical Cases, Proc. Staff Meet., Mayo Clin. **21**:246-255, 1946. Waugh, T. R., and Harding, E. W.: Heterotopic Pancreatic Tissue in the Region

The symptoms are described as those of peptic ulcer, cholecystitis or malignant growth or as indeterminate. We find it rather difficult to understand the mechanism of distress in such cases and have attributed the symptoms to concomitant disease or functional disturbances. Barbosa and others [126] analyzed 470 recorded cases. The ratio of males to females was almost 3 to 1. The commonest location was in the stomach, duodenum and jejunum, in which the incidence was almost 70 per cent. In 61 per cent, pancreatic heteropia was considered of clinical significance. Hypoglycemia and hyperinsulinism have been observed with heteropic pancreatic tissue, presenting both benign and malignant change in its insular portion.

Brucellosis and Peptic Ulcer.—The coexistence of brucellosis and peptic ulcer is not remarkable.[127]

Recurrence.—Moutier [128] reports 2 well illustrated instances of gastric ulcer recurring at the same site.

In a study of the recurrence rate in 151 patients with peptic ulcer proved by roentgenologic study placed on a standard conservative medical regimen consisting of a bland diet with six feedings daily, with the use of belladonna, phenobarbital and alumina gel, 10 per cent received no relief from symptoms; a recurrence of symptoms was noted in an average of 5 per cent per month. At the end of the first year two thirds of the group had evidence of recurrence. At the end of the second year two thirds of the remaining group also had recurrence. This is a challenging report. Almost any medical regimen should give a better result than this; the old Sippy program certainly did better; more statistical analyses of this type are greatly needed.[129]

Medical Management.—Morrison [130] fed patients with uncomplicated peptic ulcer gastric juice obtained from normal persons and neutralized, filtered and preserved with tricresol. Relief of symptoms and prompt disappearance of the crater shown in the roentgenogram ensued. The author thinks a "protective principle" is elaborated within

of the Pyloric Orifice: A Radiological and Pathological Analysis of Five Cases of Clinically Suspected Peptic Ulcer in Which Only Pancreatic Rests Were Found, Gastroenterology **6**:417-435, 1946.

126. Barbosa, J. J. de C.; Dockerty, M. B., and Waugh, J. M.: Pancreatic Heterotopia, Surg., Gynec. & Obst. **82**:527-542, 1946.

127. Carryer, H. M., and Prickman, L. E.: Brucellosis and Peptic Ulcer, Proc. Staff Meet., Mayo Clin. **21**:11-15, 1946.

128. Moutier, F.: L'ulcère gastrique récidivant "in situ" à mutation anatomique et évolutive, Arch. d. mal. de l'app. digestif **34**:101-111, 1945.

129. Raimondi, P. J., and Collen, M. F.: Recurrence Rate of Symptoms in Peptic Ulcer Patients on Conservative Medical Treatment, Gastroenterology **6**:176-181, 1946.

130. Morrison, L. M.: I. Peptic Ulcer Disappearance After Feedings of Normal Human Gastric Juice, Am. J. Digest. Dis. **12**:323-327, 1945.

the gastric and duodenal mucous membranes and secreted into the gastric juice. There are no control studies.

Twenty-six patients with peptic ulcer, in 12 of whom it was duodenal, in 5 combined duodenal and gastric, in 7 gastric, in 1 suspected marginal and in 1 confirmed marginal, comprise the series treated by the hyperalimentation program of Co Tui.[131] Three hundred to 400 Gm. of amigen were administered daily during the waking hours in eight or nine equal feedings. The regimen was continued for two to three weeks. Supplementary measures consisted in administration of multiple vitamins and intramuscular injections of liver extract (15 units twice weekly). Pain and epigastric distress disappeared in twelve to twenty-four hours, and vomiting was relieved in 7 of 13 patients within forty-eight hours. The beneficial effects are attributed to the antacid effect of the hydrolysate and to the improved synthesis of tissue. Follow-up studies revealed the treatment to be as effective, but not more effective, than other forms of therapy in relation to recurrence of symptoms. Here again control studies are lacking. There is nothing in this report to warrant the furor with which it was received by the lay press and by the public, aided and abetted by detail men.

Anion exchange resins, such as "amberlite IR-4" (a polyamine-formaldehyde resin), have great speed of action, great neutralizing power, complete inhibition of pepsin activity, absence of phosphate ion removal, no acid rebound, no constipating effect and no chloride removal, as determined by Martin and Wilkinson.[132] The p_H of 50 cc. of gastric juice was brought from 1.0 to 5.0 by 1 Gm. of resin.

The historical background of enterogastrone, anthelone and urogastrone is traced by Sandweiss.[133] Anthelone, found in the urine of normal patients, differs from urogastrone in its effect on the Mann-Williamson ulcer in that it does not inhibit gastric secretion of acid but promotes fibroblastic proliferation, new formation of blood vessels and epithelization of the mucosa. Urogastrone, also found in urine, is a more potent gastric secretory depressant than enterogastrone, prepared from the duodenal mucosa of hogs. Enterogastrone seems to have a depressant effect on gastric secretion and motility as well as an antiulcer effect similar to anthelone. It is possible that urogastrone may manifest some properties of anthelone if administered in sufficiently large doses. We confess that we are not yet satisfied with the evidence purporting

131. Co Tui; Wright, A. M.; Mulholland, J. H.; Galvin, T.; Barcham, I., and Gerst, G. R.: The Hyperalimentation Treatment of Peptic Ulcer with Amino Acids (Protein Hydrolysate) and Dextri-Maltose, Gastroenterology 5:5-17, 1945.

132. Martin, G. J., and Wilkinson, J.: The Neutralization of Gastric Acidity with Anion Exchange Resins, Gastroenterology 6:315-323, 1946.

133. Sandweiss, D. J.: Enterogastrone, Anthelone and Urogastrone: A Review of the Literature and a Suggestion for the Organization of a National Committee for the Study of "Peptic" Ulcer, Gastroenterology 5:404-415, 1945.

to show these alleged differences between the three substances in so far as their effect on gastric secretion and the healing of peptic ulcer is concerned.

Partial Gastrectomy.—Partial gastrectomy is certainly indicated in those cases of gastric ulcer in which the differentiation between benign and malignant ulcer is difficult, as in the 2 cases reported by Kiernan and Larson.[134]   King [135] performed a modified Hofmeister operation in 75 consecutive cases, with no deaths.   Lahey [136] favors a subtotal gastrectomy in all cases of gastric ulcer, provided the patient is a reasonably good risk.

Sanders [137] reports a study of three hundred and fifty operations done on 1,147 patients with peptic ulcer. Resections were done in 104; in the last 101 the mortality was 3 per cent. The indications for resection for gastric ulcer include chronic perforation, repeated hemorrhage, obstruction and extensive gastritis. Sanders also favors resection for uncomplicated gastric ulcer, pointing out that in 22 per cent of his cases of gastric cancer a preoperative diagnosis of ulcer had been made. Resection is recommended for duodenal ulcer in the presence of recurrent hemorrhage, obstruction, persistent pain or reactivation of the ulcer.

Counsellor [138] reports that at the Mayo Clinic from 1928 to 1943 there was a decrease in the number of surgically treated duodenal ulcers from approximately 38 per cent to 12 per cent, operation being reserved for those with obstruction, perforation, hemorrhage and intractable pain. Partial gastrectomy and gastroenterostomy were done with equal frequency during 1943. Sixty per cent of patients with gastric ulcer received surgical treatment. Hinton [139] believes that when surgical treatment for chronic duodenal ulcer is indicated the lesion should be removed in toto.

Digestive disturbances following partial gastrectomy have received considerable attention. Berkman and Heck [140] review the literature and recommend a high protein diet because of the hypochromic anemia occa-

134. Kiernan, P. C., and Larson, R.: Small Ulcerating Lesions of the Stomach: Report of Two Cases, Proc. Staff Meet., Mayo Clin. **21**:218-223, 1946.

135. King, M. M.: Subtotal Gastrectomy in the Treatment of Ulcer, Am. J. Surg. **71**:350-354, 1946.

136. Lahey, F. H.: Gastric Surgery, New England J. Med. **234**:809-822, 1946.

137. Sanders, R. L.: A Review of One Hundred and One Subtotal Gastrectomies for Benign Ulcers, Surgery **18**:229-237, 1945.

138. Counsellor, V. S.: Surgery of the Stomach and Duodenum, S. Clin. North America **25**:891-902, 1945.

139. Hinton, J. W.: The Surgical Treatment of Chronic Duodenal Ulcer, Bull. New York Acad. Med. **22**:227-236, 1946.

140. Berkman, J. M., and Heck, F. J.: Symptoms Following Partial Gastric Resection, Gastroenterology **5**:85-95, 1945.

sionally seen. Custer, Butt and Waugh [141] consider the dumping syndrome to be a definite clinical, and probably physiologic, entity occurring after gastroenterostomy either with or without gastric resection. The incidence after resection is from 5 to 12 per cent. Since it apparently results from rapid dumping of food from the stomach into the unprepared jejunum, it is well named. When dumping once has become established, it is apt to be permanent, since it probably is related directly to the size of the anastomotic stoma.

The results of operations that narrow the opening of the gastric remnant have been uniformly good. Reoperation has not been undertaken, but it is suggested that this procedure be considered in some of the severe cases. A medical regimen is outlined.

In order to determine the degree of disturbance in digestion, Wollaeger and his associates [142] first measured the total fat and nitrogen content in the feces of 6 adult subjects in good health and in that of patients with duodenal ulcer, all of whom were given the same diet high in fat (208 Gm. daily). There was no significant difference in these two groups, although with a uniform dietary intake the fecal components varied considerably. The fecal solids ranged from 15.5 to 40.4 Gm. per day, with an average of 26.6 Gm. Fecal fat (ether-soluble fraction) varied from 5.5 to 13.6 Gm. per day, with an average of 8.7 Gm. Fecal nitrogen content varied from 0.6 to 1.9 Gm. per day, with an average of 1.2 Gm. Determination of the total fecal solids, without regard for the amount of fat ingested, would not be a satisfactory test for steatorrhea. In spite of the high intake of fat (208 Gm., with 97.5 Gm. of protein and 140.5 Gm. of carbohydrate), relatively little fat was lost in the feces. The maximal loss of calories was 6 per cent of those ingested. Fourteen patients who had undergone partial gastrectomy were studied. In 10 given the same diet the daily excretion of fat exceeded that of normal people and of patients with duodenal ulcer. Four patients received only half the amount of fat given the first group (104 Gm.), but each of them lost a greater percentage of ingested fat than did any of the controls. In most instances, however, the amount of fat excreted was relatively small. The loss was largest in patients with abdominal distress after meals (without peptic ulceration).[143]

141. Custer, M. D.; Butt, H. R., and Waugh, J. M.: The So-Called "Dumping Syndrome" After Subtotal Gastrectomy: A Clinical Study, Ann. Surg. **123**:410-418, 1946.

142. Wollaeger, E. E.; Comfort, M. W.; Weir, J. F., and Osterberg, A. E.: The Total Solids, Fat and Nitrogen in the Feces: I. A Study of Normal Persons and of Patients with Duodenal Ulcer on a Test Diet Containing Large Amounts of Fat, Gastroenterology **6**:83-92, 1946.

143. Wollaeger, E. E.; Comfort, M. W.; Weir, J. F., and Osterberg, A. E.: The Total Solids, Fat and Nitrogen in the Feces: II. A Study of Persons Who Had Undergone Partial Gastrectomy with Anastomosis of the Entire Cut End of the Stomach and the Jejunum (Polya Anastomosis), Gastroenterology **6**:93-104, 1946.

Of interest in this connection is the report by Richardson[144] of a jejunocolic fistula with a fatty diarrhea and anemia of a high color index type. Closure of the intestinal fistula relieved the fatty diarrhea and the anemia.

Complications of Gastroenterostomy.—Gray and Sharpe[145] made a comparative study of two groups of one hundred consecutive cases in which posterior gastroenterostomies were performed for duodenal ulcer. The factors of age, sex, activity of lesion, position of stoma and technical skill were fairly constant. Because of the high incidence of postoperative retention in group 1, changes in the technic of operation and postoperative care were made for group 2 in order to combat postoperative jejunitis, to promote peristalsis and to avoid overloading the stomach. These changes consisted in the use of three rows of sutures instead of two as well as the postoperative regulation of intake of fluid and the administration of medicaments such as tablets of aluminum hydroxide gel, neostigmine methylsulfate, phenobarbital, atropine, diphenyl acetic acid and diethylaminoethanol. A comparison of the two groups revealed that the incidence of retention of any degree decreased from 35 per cent in group 1 to 19 per cent in group 2 and the incidence of serious retention (persisting longer than five days) from 24 to 13 per cent. In the first group 6 patients were subjected to secondary operation and in the second group none.

Regurgitant vomiting is of two general types: (1) the vomiting that develops immediately after operation, suggesting mechanical obstruction, (2) the vomiting that develops on the sixth to tenth day after operation, occurring most probably because of stomal edema and inflammation. For the first type some further operative procedure is frequently necessary; for the second type supportive measures, involving a knowledge of the principles of blood chemistry and fluid balance, are usually sufficient.

Marshall,[146] over a five-year period (1941 to 1945), performed sixty-nine resections for gastrojejunal ulcer in a group of two hundred and eighty-nine consecutive resections for peptic ulcer. Sixty of the gastrojejunal ulcers had developed after gastroenterostomy, five after inadequate resection and four after the Finsterer prepyloric resection method. Fazio[147] reports the perforation of a duodenal ulcer fifteen days after gastroenterostomy.

144. Richardson, J. E.: Addisonian Anaemia Following Entero-Anastomosis, Brit. J. Surg. **33**:71-74, 1945.

145. Gray, H. K., and Sharpe, W. S.: Gastric Retention After Posterior Gastro-Enterostomy for Duodenal Ulcer: Prevention and Treatment, Ann. Surg. **123**:397-409, 1946.

146. Marshall, S. F.: The Problems of Gastrojejunal Ulcer with Illustrative Case Reports, S. Clin. North America **26**:751-762, 1946.

147. Fazio, J. M.: Ulcera péptica post-gastroenteroanastomosis perforada en peritoneo libre, Rev. Asoc. méd. argent. **59**:1109-1111, 1945.

In a clinical and pathologic study of 100 cases of gastrojejunal ulcer treated by resection, Tosseland and McDonald[148] found parietal cells in the gastric mucosa adjacent to the stoma in the majority of cases. In 81 of 87 cases the ulcer occurred on the jejunal side, in 3 on the gastric side and in 3 on the anastomotic line. Simple epithelial cells were found at or near the anastomotic line in approximately one fifth of the cases. Brunner's glands were found occasionally in the jejunal mucosa adjacent to the stoma. While gastrojejunitis, moderate to severe, was usually present, there was little or no correlation between the severity of symptoms and the degree of inflammation. Suture material and magnesium silicate were found in the region of the stoma but appeared to have little direct relationship to the ulcer.

Ransom[149] reports fourteen late postoperative gastrojejunocolic fistulas. The intervals between the original operation for ulcer and the entry into hospital for fistula varied between one and twenty-six years, with an average of nine and a half years. Nearly all patients required intensive preoperative care for nutritional disturbances. Ten were treated with a restorative type of operation, with 1 death; of the 9 surviving, recurrent ulcer developed in 5, 3 requiring further surgical treatment. Partial gastrectomy was performed in 4 cases, with 1 death and no recurrence of symptoms in the 3 survivors.

Vagotomy.—In a survey of the present status of vagotomy, Dragstedt[150] reports data concerning thirty duodenal ulcers, two gastric ulcers and seven gastrojejunal ulcers treated with vagal section. There was a striking and persistent relief of distress, with gain in weight and roentgenographic evidence of healing of the lesions. Thornton, Storer and Dragstedt[151] discuss the effects of supradiaphragmatic section of the vagus nerves on gastric secretion and motility in 38 patients with peptic ulcer. The continuous nocturnal fasting secretion in patients with ulcer was found to be much greater than that in control groups. The hypersecretion, considered chiefly neurogenic in character, is much reduced by vagal section. The empty stomach of patients with ulcer often displays a hypertonicity and hypermotility with exaggerated hunger contractions; these return toward the normal state after bilateral vagotomy. Complete section of the vagus nerves abolishes the secretion of gastric juice produced by a sham meal or by insulin-induced hypoglycemia, but it has little or no effect on the

148. Tosseland, N. E., and McDonald, J. R.: Ulcerating Lesions of the Gastroenteric Stoma, Arch. Surg. **51**:113-119 (Sept.) 1945.

149. Ransom, H. K.: Gastrojejunocolic Fistula, Surgery **18**:177-190, 1945.

150. Dragstedt, L. R.: Vagotomy for Gastroduodenal Ulcer, Ann. Surg. **122**:973-989, 1945.

151. Thornton, T. F., Jr.; Storer, E. H., and Dragstedt, L. R.: Supradiaphragmatic Section of the Vagus Nerves, J. A. M. A. **130**:764-771 (March 23) 1946.

response to histamine or caffeine. The absence of a secretory response to a sham meal or to insulin-induced hypoglycemia is considered to be good evidence of complete vagal section.

Arterial Ligation.—A different surgical approach is provided by Somervell,[152] who reports over 380 cases of duodenal ulcer treated by gastroenterostomy and ligature of the arteries of the stomach. The patients were inhabitants of Travancore, India, where duodenal ulcer is extremely common and the average acidity high. Patients with normal or only slightly increased acidity and a fasting gastric juice with a total acidity of under 60 were treated ordinarily with gastro-enterostomy alone. When the fasting free acidity was above 60, gastroenterostomy was combined with ligature of the arterial supply of the stomach. The commonest operative procedure is to ligate firmly about five out of every six of the small branches of the large arteries supplying the greater curvature on its anterior and posterior aspects. The sheaf of vessels on the lesser curvature is ligated in toto. The arteries at the pylorus and within an inch of it need not be tied. The usual effect of such ligature is an immediate and considerable drop in the acidity of the stomach, although occasionally the operation fails to depress acidity. Somervell attributes failure to inadequate ligation of the arterial supply or to ligation of the veins with the arteries. Postoperative studies indicate that patients treated with arterial ligation with or without gastroenterostomy exhibit a pronounced diminution in acid secretion three weeks after operation and that the same diminution is present one to five years later. Ligation proved superior to gastrectomy in the prevention of recurrent gastrojejunal ulcer. Gastro-scopic examination of such patients by Freeman[153] before and six months after gastric arterial ligature had been performed revealed that the mucosa had undergone a striking transmutation from the hyperplastic state, found particularly in those with obstruction, to a normal state. Wood[100] subscribes to the view that the control of acid gastric juice is the basis of therapy today and reports his results in 42 cases of duodenal ulcer treated by the ligature method of Somervell. An immediate reduction in free acidity occurred in most cases. The results are not conclusive, but in the brief period of postoperative observation they seem encouraging.

Urinary Chloride in Pyloric Obstruction.—The amount of chloride in the urine is considered a more reliable index of chloride balance than the plasma chloride content. In 80 per cent of 50 cases of

152. Somervell, T. H.: Physiological Gastrectomy: The Operation of Ligature of the Arteries of the Stomach to Relieve Hyperacidity and to Prevent Recurrent Ulceration After Gastro-Enterostomy, Brit. J. Surg. **33**:146-152, 1945.

153. Freeman, H.: Duodenal Ulceration: A Gastroscopic Study of the Gastric Mucosa and Its Surgical Significance, Brit. M. J. **1**:980, 1946.

duodenal ulcer with obstruction notable diminution of the urinary chloride content was present, although the plasma chloride content was normal. The chloride in the tissues undergoes depletion in order to maintain a normal blood level. In 60 per cent of patients there was a severe alteration in the acid-base balance of the blood; 40 per cent had alkalosis and 20 per cent had acidosis. Azotemia was present in more than 60 per cent. Hypochloruria together with nitrogen retention and disturbances in the acid-base balance constitutes the outstanding biochemical feature in patients with pyloric obstruction. To supply the needed salt and water, administration of large amounts of 3 per cent isotonic solution of sodium chloride is advised, the amount required being indicated by determinations of the urinary chloride.

Twenty patients were relieved by medical therapy alone. Thirty were treated surgically after restoration of the acid-base balance. The time for surgical intervention from the chemical point of view was determined by a normal urinary excretion of chloride of more than 5 Gm. in twenty-four hours (Volhard-Hardy procedure). The total urinary excretion should be at least 1,500 cc. in twenty-four hours, with a normal specific gravity.[154]

Acute Perforation.—In 96 cases reported by Black and Blackford [155] 92 involved men and 4 involved women. The mortality in the 24 patients less than 40 years of age was 4 per cent, in the 33 in the fifth decade 12 per cent and in those more than 50 years of age 18 per cent. Eighty-seven perforations were duodenal, six gastric and three pyloric. Forty-six patients were operated on six hours after perforation, with a mortality of 11 per cent, 28 in the second six hours, with a mortality of 7 per cent, 12 between twelve and twenty-four hours and 5 after more than twenty-four hours, with a mortality in these two groups of 25 per cent. Eighty-three of the group gave a previous history of peptic ulcer. Closure of the perforation alone was attended by the lowest postoperative mortality; this was the treatment of choice.

Sandberg's[156] statistics on 110 patients (101 of them men) are similar. Free gas was demonstrated roentgenologically in the abdominal cavity in 73 per cent. The mortality for the series was 10.9 per cent; for those operated on it was 9.5 per cent. In 68 cases operation was performed within six hours of onset, with a mortality of 5.9 per cent;

154. Sanchez-Vegas, J., and Collins, E. N.: Importance of Urinary Chloride Determinations in Treatment of Patients Having Pyloric Obstruction: A Review of Fifty Cases of Duodenal Ulcer, Am. J. M. Sc. **211**:428-436, 1946.

155. Black, B. M., and Blackford, R. E.: Perforated Peptic Ulcer: Review of Ninety-Six Cases, S. Clin. North America **25**:918-928, 1945.

156. Sandberg, I. R.: On the Treatment of Perforated Gastric and Duodenal Ulcer, Acta chir. Scandinav. **93**:467-482, 1946.

in 28 the interval was six to twelve hours, with a mortality of 10.7 per cent.

Of 54 cases followed for two to five years after operation, data were obtained in 51. Four patients died of another disease. Forty per cent were symptom free after suture or excision plus suture, 20 per cent had mild symptoms and in 40 per cent the result was unsatisfactory.

Forty [157] found 17 deaths in a series of one hundred perforations treated by simple suture. The after-history of 70 of the 83 surviving patients was studied for periods up to five years. A recurrence of digestive symptoms occurred in 38, severe enough in 14 to require readmission to the hospital. The rate of recurrence of symptoms was highest in patients who had suffered longest from their ulcer before operation. In the 70 patients studied, roentgenologic evidence of recurrent or persistent ulcer was found in 43. Ten secondary operations were performed, with 2 deaths.

Illingworth and others [158] report a study of 733 patients who survived operation for perforation; 666 could be traced. Remission of symptoms was seldom of long duration. Within one year, 40 per cent of the patients had relapsed (symptoms were mild in 20 per cent and severe in 20 per cent). After five years, 70 per cent had relapsed (symptoms were mild in 20 per cent and severe in 50 per cent). The incidence of major complications such as reperforation, hemorrhage or other symptoms requiring elective operation was 20 per cent within five years. The mortality rate among survivors from perforation was somewhat higher than the standard mortality rate. The progress among survivors was best in the old and worst in the young patients. Anderson, Allen and Packard [159] report essentially similar results.

Kadish and Rivers [160] describe an ulcer perforating into the gallbladder, without abdominal complaints. Pain was present in the right lower portion of the chest.

Ulcer in Military Service.—Garbat [161] discusses exhaustively the medical problem of peptic ulcer among the military forces, outlining

157. Forty, F.: One Hundred Cases of Perforated Peptic Ulcer, with an Analysis of Immediate and Remote Results of Simple Closure, Brit. M. J. **1**:790-793, 1946.

158. Illingworth, C. F. W.; Scott, L. D. W., and Jamieson, R. A.: Progress After Perforated Peptic Ulcer, Brit. M. J. **1**:787-790, 1946.

159. Anderson, R. H.; Allen, G. L., and Packard, G. B.: Factors Influencing the Prognosis in Acute Perforated Peptic Ulcer Based on a Review of Fifty-Nine Consecutive Cases at the Colorado General Hospital, Rocky Mountain M. J. **42**: 661-665, 1945.

160. Kadish, A. H., and Rivers, A. B.: Pain in the Perforating Type of Peptic Ulcer, J. A. M. A. **130**:570-571 (March 2) 1946.

161. Garbat, A. L.: Problems of Peptic Ulcer in the Armed Forces and in the Returned Soldiers, New York State J. Med. **46**:894-901, 1946.

its treatment both organically and psychosomatically. Twiss and Par-
sonnet [162] report 82 consecutive cases of peptic ulcer in naval personnel;
in 72 it was duodenal and in 10 gastric. In 55 per cent the ulcers
were incurred before enlistment. No patient with peptic ulcer should
be admitted to the armed forces; early separation from service is
recommended in all cases. Reeser and Guthrie [163] report that in
200 men in the army with peptic ulcer the lesion was located in the
duodenum in 185 and in the stomach in 13; in 2 both gastric and
duodenal ulcers were present. In 73 per cent the symptoms antedated
military service and in 27 per cent they developed in line of duty;
81.5 per cent were separated from service.

Hall [164] discusses the diagnosis of peptic ulcer in difficult circum-
stances such as the following: (1) peptic ulcer manifested by atypical
symptoms, (2) the ulcer symptomatology in the absence of ulcer,
(3) suggestive gastrointestinal symptomatology in the presence of duo-
denal deformity of old ulceration and (4) peptic ulcer in association
with other pathologic processes. Harrell and Wilson [165] report 66 cases
of peptic ulcer (0.3 per cent) in a group of 22,000 persons admitted
to a hospital in Panama. In 10 patients (0.045 per cent) the ulcer
had perforated on admission. All were operated on, with no mortality.

McCarthy and Knoepp [166] report that of 92,094 patients admitted
to the hospital in 629 (0.68 per cent) the condition was diagnosed
as peptic ulcer. The incidence of perforation was 4.4 per cent. Fifty-
nine and three tenths per cent of all patients with ulcer were dis-
charged from the service because of the consequent disability; 80.8 per
cent of the patients with perforated ulcers were discharged. The
average duration from the time of onset to the time of operation was
14.3 hours. The complications were peritonitis (27.7 per cent),
femoral phlebothrombosis (3.9 per cent), disruption of the wound
(3.9 per cent), pneumonia (11.5 per cent) and empyema (3.9 per cent).
There was 1 death, a mortality of 3.57 per cent, in 28 cases.

Beaver and others [167] describe a perforated duodenal ulcer in a
27 year old soldier, noteworthy for its complications, which included

162. Twiss, J. R., and Parsonnet, E. V.: Practical Aspects of Peptic Ulcer
Management Under Service Conditions, J. A. M. A. **129**:857-863 (Nov. 24) 1945.

163. Reeser, R., Jr., and Guthrie, M. B.: The Management of Army Personnel
with Peptic Ulcer: An Analysis of Two Hundred Cases, Mil. Surgeon **98**:125-
131, 1946.

164. Hall, J. W., Jr.: Benign Peptic Ulcer as a Diagnostic Problem, Mil.
Surgeon **98**:119-125, 1946.

165. Harrell, W. B., and Wilson, R. O.: Ruptured Peptic Ulcer Among
U. S. Troops in Panama, Mil. Surgeon **96**:336-342, 1945.

166. McCarthy, A. M., and Knoepp, L. F.: Perforated Peptic Ulcer: A
Series of Twenty-Eight Cases, Am. J. Surg. **71**:260-266, 1946.

167. Beaver, M. G.; Davis, P. B., and Smith, R. S.: Hepatic Abscess Secondary
to Perforated Duodenal Ulcer, Northwest Med. **45**:94-96, 1946.

suppurative peritonitis associated with an infection of the wound and resultant incisional hernia, two attacks of acute pneumonitis, acute pleural effusion, femoral thrombophlebitis and a pyogenic abscess of the liver, with draining sinuses persisting after the acute hepatic infection had subsided. In five months the patient received 24,635,000 units of penicillin by intramuscular injection. The infecting organism was a penicillin-susceptible hemolytic Staphylococcus aureus; this therapy was considered of utmost value during the acute phases. Healing of the tortuous sinus tract in the right upper area of the abdomen did not occur until a mechanically perfect system of drainage had been established by surgical procedures.

BENIGN TUMORS

Scott and Brunschwig [168] describe submucosal lipomas as variable in size, sessile or pedunculated and located frequently in the pylorus. The mucosa overlying the tumor is usually smooth, but ulceration is not uncommon. A fairly constant feature is the stretching of the adjacent rugae to bridge the space between the top of the tumor and the surrounding mucosa. The clinical picture resembles that of other benign gastric tumors. In the case reported the carcinoma was a coincidental finding. Moricheau-Beauchant and others [169] record another intragastric lipoma. In the case described by Hobbs and Cohen [170] a lipoma acted as the propulsive factor for the invagination into the duodenum of three fourths of the stomach. Forty-one instances of intussusception are compiled from the literature.

Two leiomyomas and a hemangioendothelioma are reported by Sherman, Long and Caylor.[171] Hillemand and Porcher [172] found a pedunculated tumor to be a glandular epithelioma. Paul and Chapman [173] report the gastroscopic appearance of a localized tumor of the anterior wall of the stomach, proved histologically to be a neurofibroma. A tumor 5 cm. in diameter in the lesser curvature of the stomach proved histologically to be a schwannoma, according to Burlando and

168. Scott, O. B., and Brunschwig, A.: Submucosal Lipomas of the Stomach: A Review of the Literature and Report of a Case Associated with Carcinoma, Arch. Surg. **52**:253-259 (March) 1946.

169. Moricheau-Beauchant, J.; Debellert, J., and Payard, J. M.: Image radiologique d'une tumeur intragastrique, Arch. d. mal. de l'app. digestif **35**:52-54, 1946.

170. Hobbs, W. H., and Cohen, S. E.; Gastroduodenal Invagination Due to a Submucous Lipoma of the Stomach, Am. J. Surg. **71**:505-518, 1946.

171. Sherman, R. M.; Long, L., and Caylor, H. D.: Unusual Tumors of the Stomach, Am. J. Surg. **71**:657-663, 1946.

172. Hillemand, P., and Porcher, P.: A propos du diagnostic des tumeurs pédiculées gastriques, Arch. d. mal. de l'app. digestif **34**:130-131, 1945.

173. Paul, W. D., and Chapman, D. W.: Neurofibroma: A Gastroscopic Report, Am. J. Digest Dis. **12**:258-260, 1945.

others.[174]   D'Allaines and his associates [175] report two benign tumors located in the pyloric canal.

Strassmann [176] reports the accidental finding at autopsy of an adenoacanthoma of the stomach associated with hypertrophic gastritis. The metastases in the liver and in regional lymph nodes were due to pure squamous cell carcinoma with many cornified pearls.

HODGKIN'S DISEASE

Two instances of isolated Hodgkin's disease of the stomach described by Browne and McHardy [177] are the twenty-first and twenty-second reported in the literature. Sluggish peristalsis and infiltration of the greater curvature suggested lymphogranulomatosis to the roentgenologist.

174. Burlando, A.; Saccone, R., and Zavatarelli, E.:   Un caso de schwannoma del estomago, Rev. Asoc. méd. argent. **60**:453-456, 1946.

175. d'Allaines, F.; Lambling, A., and Debusscherre, F. N.:   Tumeurs bénignes du canal pyloro-duodénal, Arch. d. mal. de l'app. digestif **34**:156-158, 1945.

176. Strassmann, G.: Adenoacanthoma of the Stomach, Arch. Path. **41**:213-219 (Feb.) 1946.

177. Browne, D. C., and McHardy, G.:   Isolated Hodgkin's Disease of the Stomach, Gastroenterology **6**:596-601, 1946.

(To Be Concluded)

Correspondence

ERYTHEMA EXUDATIVUM MULTIFORME OF HEBRA AND OF OSLER

To the Editor:—Dr. E. Rose (ARCH. INT. MED. **79**:360 [March] 1947) has criticized the Commission on Acute Respiratory Disease for failure to include in the differential diagnosis of erythema exudativum multiforme the group of cases which Osler published many years ago under the title "On the Visceral Complications of Erythema Exudativum Multiforme" (*Am. J. M. Sc.* **110**:629 [Dec.] 1895). Dr. Rose stressed the similarity of title in the diseases described by von Hebra and by Osler, although he fully realized that the two conditions are different. Whereas the need for this differential diagnosis is undoubtedly true, the comments of Dr. Rose indicate an appraisal of the Osler group of cases which is not supported by the historical data or by the contents of the paper to which he referred. Since Osler is an important historical figure in medicine, it seems fitting to attempt a more complete appraisal of his work in this field.

Von Hebra was the first to use the term erythema exudativum multiforme to designate as one entity a wide variety of cutaneous manifestations that had been recorded under different titles in the books on dermatology of his period and long before (On Diseases of the Skin, London, New Sydenham Society, 1866, vol. 1, p. 285). It is true that he did not describe all the important features of this disease, but his concept represented an important advance. The term multiforme referred to the polymorphous appearances in the eruption as a whole either in the same or in different attacks as well as to the various changes that might be observed in a single lesion in its course of development. This is the entity with which the Commission on Acute Respiratory Disease was chiefly concerned.

Osler's contributions really began in 1888, and his last paper appeared in 1914. The following titles will show the evolution in his concept: (*a*) On a Form of Purpura Associated with Articular, Gastro-Intestinal and Renal Symptoms, *New York M. J.* **48**:675, 1888; (*b*) On the Visceral Complications of Erythema Exudativum Multiforme, *Am. J. M. Sc.* **110**:629, 1895; (*c*) The Visceral Lesions of the Erythema Group, *Brit. J. Dermat.* **12**:227, 1900; (*d*) On the Visceral Manifestations of the Erythema Group of Skin Diseases, *Am. J. M. Sc.* **127**:1, 1904; (*e*) On the Surgical Importance of the Visceral Crises in the Erythema Group of Skin Diseases, ibid. **127**:751, 1904; (*f*) The Visceral Lesions of Purpura and Allied Conditions, *Brit. M. J.* **1**:517, 1914.

The first paper presented little that was different from the entity described so well by Henoch. The second paper, however, represented a distinct advance in that a consideration of cutaneous manifestations other than purpura was included, and here one gets the first inkling of why Osler used the same title, erythema exudativum multiforme, as did von Hebra. This is the paper to which Dr. Rose refers, and an examination of it shows that Osler was dealing practically always with the same entity which had been previously called Henoch's purpura but to which Osler added the lesions resembling "erythema multiforme." Perhaps 1 case, possibly 2, may not belong in the same category, but the rest of the 11 cases presented the same monotonous clinical picture, with some slight variations. To me at least this is a reasonably homogeneous group of cases. The third paper shows a new title again—"the erythema group." Here Osler said: "It was really

very difficult to find a name under which to group the cases." Yielding to the criticisms of his friends in the dermatologic field, although sensing that their criticisms were not entirely clear, Osler dropped the term erythema exudativum multiforme and substituted the name "the erythema group." I am not certain, that this group of 7 new cases was homogeneous in type. Indeed, his case 13 may have been an example of Hebra's erythema exudativum multiforme, with coincidental colicky attacks in a person who had been recently subjected to surgical removal of an ovarian tumor; however, the data do not permit an accurate evaluation, and Osler may have interpreted the case correctly. In this paper the concluding sentence explains why his concept, if not already heterogeneous, was destined to become so, for he said that there is "a positive advantage in recognizing the affinities and the strong points of similarity in affections usually grouped as separate diseases." In the fourth paper Osler's group of cases had definitely become heterogeneous; thus his cases 19 and 26 were classic examples of systemic lupus erythematosus. Osler himself said: "A criticism has been made of my previous papers that I had jumbled together a motley group of cases, some purpura, some of angioneurotic edema, others of peliosis rheumatica; and still others again of exudative erythema. I did so on purpose, for I was seeking similarities, not diversities, and I refrained as much as possible from the use of specific terms, often, indeed, not knowing what to call a case watched for a long period." In his fifth paper Osler stressed the surgical importance of the "erythema group," but it should be noted that his remarks applied chiefly to cases of what can be called the Osler-Henoch-Schönlein disease. The general purpose of this article was to point out the frequency with which this condition could be mistaken for appendicitis, intussusception, obstruction of the bowel, renal colic and other conditions. Osler said: "So far as I know, it (meaning colic) is never dangerous. In no case recorded has death resulted, I believe, from intestinal causes." This statement needs to be modified, and, indeed, Osler himself referred to one of Sutherland's cases in which death occurred from peritonitis following intussusception. Nevertheless, this paper represented probably the beginning of a better evaluation of the difficulties in the diagnosis of the surgical complications of this disease. In the sixth and final paper the title reverted once more to purpura as the main theme, along with the allied conditions. The heterogeneity of the concept is now obvious, but despite this there is no doubt that the paper will prove to be classic in the sense of fine Hippocratic observation. In it is detailed an enormous clinical experience of cases which were interpreted as involving analogous changes in the skin and internal organs. Moreover, Osler mentioned the possibility that the acute renal alterations could pass over into the subacute and chronic stages with their attendant consequences. There are many other observations of wide interest in this paper, and it is so well written that one can, for the most part, readily classify the cases in their proper categories. That Osler had kept abreast of the time is shown by the following comment: "Before long the anaphylactic key will unlock the mysteries of these cases." Today, more than thirty years later, this prophesy has not yet been fulfilled, although an offshoot of this concept is the one most widely held.

Osler's reputation has been often considered as dependent on his personal attributes, his educational views and his teaching ability. These papers, among many others, point to his influence as a great clinician who contributed much to clinical medicine. This group of cases was a source of inspiration to many who were interested in the relation of dermatology to internal medicine and vice versa, and among these may be mentioned Emanuel Libman, who was impressed by the

importance of these papers and often cited them as models. Heterogeneous as his concept later proved to be, Osler added much to the concept of a special type of disease which can be conveniently called the Osler-Henoch-Schönlein disease. From the clinical point of view little can be added aside from a better description of the cutaneous lesions. Osler stressed the important principle that the skin may show changes that are the counterpart of those in the internal organs, if not pathologically, at least clinically; for, it should be noted, Osler himself never reported any postmortem observations in his own cases. It should also be stressed that in none of the cases detailed by Osler was there evidence of rheumatic fever in the sense of the Aschoff body.

There are two important lessons of historical value that can be drawn from a study of Osler's papers. First, the attempt to find similarities led to the establishment of a heterogeneous concept. This should teach us that attempts, whether clinical, pathologic or experimental, to create common denominators on the basis of a general feature, such as the simultaneous occurrence of lesions in the skin and internal organs or a similar pathogenesis, should be viewed with caution. Second, the need for close cooperation between internists and dermatologists is evident; with such cooperation knowledge of the borderline fields would have prevented some of the confusion in the selection of such terms as erythema exudativum multiforme and others.

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News and Comment

Announcement of the .1949 International Congress on Rheumatic Diseases.—A congress of La Ligue Internationale Contre le Rhumatisme, providing for meetings in New York, Philadelphia and Boston, was to have been held in the United States during 1940. This Congress was interrupted by the War. At that time a statement was distributed widely in the United States and also published in England, outlining the situation presenting and the extent to which preparations had advanced, and indicating a desire on the part of the United States to consummate the congress at the earliest opportunity after cessation of hostilities.

It is now clear, since termination of the war, that efforts are being made in many of the countries of Europe toward resumption of progressive and large scale activities in the field of rheumatic diseases, notwithstanding the many existing handicaps. Increasing numbers of groups in the various countries of Europe and in the United States and Canada are avowedly desirous of meeting each other and exchanging ideas. At this stage in the development of international cooperation, it seems of the highest importance that the medical profession, representing one of the major fields of science, lend to the situation under discussion everything within its power in order to bring together fellow workers in the same field with the aim of enabling them to know one another better, to exchange ideas and to build further toward that ideal of international understanding fundamental to any permanent peace. During the past year, a great deal of correspondence has taken place and there has been considerable personal contact between many persons . interested in rheumatic diseases who are desirous of holding an international congress as soon as possible. It seems clear that 1949 is the earliest date at which a movement of such significance can be attempted.

.The American Rheumatism Association therefore, through its appointed representatives and pursuant to the interrupted plan for 1940, officially announces to all members of La Ligue Internationale Contre le Rhumatisme its desire and intention to sponsor an International Congress for Rheumatic Diseases in the United States in the year 1949, the exact time and place to be determined later but to be approximately contemporaneous with the Annual Convention of the American Medical Association. To all interested, the association extends a most cordial invitation. As arrangements develop, appropriate additional announcements will be forthcoming.

Course in Application of Nuclear Physics to Biologic and Medical Sciences.—The University of California Medical School, in association with University Extension, University of California, announces a course in the Application of Nuclear Physics to the Biological and Medical Sciences to be given at the Medical Center, in San Francisco, from June 30 through July 18, 1947. It will consist of didactic lectures, laboratory demonstrations and seminars for round table discussions and will be open to persons in the fields of medical and biologic research.

Detailed information may be procured from Dr. Stacy R. Mettier, head of postgraduate instruction, Medical .Extension, University of California Medical Center, San Francisco 22, Calif.

Book Reviews

Synopsis of Pathology. By W. A. D. Anderson. Second edition. Price, $6.50. Pp. 741, with 327 illustrations, 15 in color. St. Louis: C. V. Mosby Company, 1946.

This second edition of the deservedly popular text first published in 1942 reveals additions and improvements in almost every chapter. One is impressed by the generally excellent black and white photomicrographs but disappointed in a number of the color plates, of which numbers 3, 6, 8, 13, 14 and 15 are particularly poor in histologic detail. One wonders why the author chose two photomicrographs to illustrate Treponema pallidum in tissues but gave no photomicrographs of syphilitic chancre or granuloma inguinale and why three photomicrographs of mesothelioma of the pleura, a rare lesion, are shown but none of the lesions observed in asthma, silicosis or lipid pneumonia, which are common. In general, however, the morphologic aspects of disease, gross and microscopic, are well described and unusually well illustrated by numerous photographs.

Statements such as that appearing on page 193, that "nearly all true aneurysms of the aorta are of syphilitic origin," should be qualified, since abdominal aortic aneurysms in elderly white persons are usually arteriosclerotic in origin. The scope of the book being considered, however, such shortcomings are infrequent, and the work as a whole compares favorably with much larger textbooks. The bibliography is to be commended in particular. The references are well chosen, written in English and of recent date. The author states that the book is designed to be useful to the medical student, to the dental student and to the clinician. This reviewer believes that the author has achieved his purpose admirably.

Journal of the History of Medicine and Allied Sciences. Published quarterly. Price, $7.50 in the United States, Canada and Latin America; $8.50 elsewhere. Single copies, $2.50. New York: Schuman's.

The ARCHIVES is always glad to welcome an attractive newcomer. This new journal of medical history appears to be well bred, charming and well dressed, which is about all that any dowager can say for a debutante.

There is need for another journal in the field of medical history. The members of the editorial board of this one are to be congratulated for what they have in mind. They propose to publish contributions on all aspects of medical history, avoiding narrow bibliographic or philologic material and cultivating broader fields. The first number contains several pleasant articles, a section labeled "Notes and Queries," which promises interesting growth, and another comprising book reviews, which is certain to be valuable. On the whole, medical libraries should certainly become subscribers to a journal so likely to prove valuable for teaching or research; and so should physicians and students who believe that familiarity with the past is the safest guide for unrolling the future wisely.

Diabetes: A Concise Presentation. By Henry J. John, M.D. Price, $3.25. Pp. 300. St. Louis: C. V. Mosby Company, 1946.

This is a readable book which discusses the modern treatment of diabetes in an interesting way. The author expresses the belief that the essential criterion for success lies in the maintenance of a nearly normal blood sugar level. He defends this thesis loyally.

The portions dealing with the composition of diets, the use of insulin and the management of complications are more orthodox but no less clearly expressed. As is stated in the preface, a good deal of the contents can be found in articles

which the author has written and published in various medical journals. It is useful, however, to have so much of his experience documented in a single volume.

Dr. William S. Middleton has added a foreword which is characteristically charming and well written. On the whole, the book is worth owning.

The Vitamins in Medicine. By Franklin Bicknell, D.M., M.R.C.P., and Frederick Prescott, M.Sc., Ph.D., A.R.I.C., M.R.C.S. Second edition. Price, $12. Pp. 916, with 208 illustrations. New York: Grune & Stratton, Inc., 1946.

This book provides a vade mecum for the physician who ought to have at hand a ready reference to the more important literature on vitamins. It is as complete a review of the subject as is feasible for this intended usefulness. Apparently nothing of much significance was omitted that was available to the authors up to the date of the completion of their task—June 1945. The first edition, which was published in 1942, has been altered rather extensively. The chapters on the vitamins of the vitamin B complex have been largely rewritten. A chapter on the "essential" unsaturated fatty acids has been added, and other material has been amplified or amended.

The rate of accumulation of information on vitamins and the fact that this information is scattered through the journals of more than a dozen special fields make it difficult for even the specialist in nutrition to keep abreast. The authors of this volume, with commendably good judgment, have analyzed some four thousand, five hundred of·the more significant publications covering the history, chemistry, food sources, physiology, pharmacology, human requirements, methods for detection of deficiencies and therapeutic uses of the vitamins. Increased familiarity on the part of the physician with the physiologic and pharmacologic basis for the use of vitamins in treatment is badly needed as an antidote to the frequently untrustworthy statements of the salesmen of vitamins from whom the average physician has received far too much of his education in this subject.

Research in Medicine, and Other Addresses. By Sir Thomas Lewis. Second edition. Price, 5s. Pp. 112. London: H. K. Lewis & Co., Ltd., 1945.

This is a second edition of a series of articles and lectures previously reviewed, the contents of which are or should be familiar to every student and teacher of medicine. To the series have been added three new addresses under the title "Reflections upon Reforms in Medical Education." A note from the publishers states that the proofs were passed for publication shortly before Sir Thomas Lewis' untimely death and that publication was delayed due to printing difficulties. The publishers hope, as all do, that "they will further the cause to which Sir Thomas Lewis devoted so much attention."

The essays for the most part revolve about the theme which Sir Thomas Lewis continued to stress throughout his life—that the problems daily encountered in medical practice are capable of solution by physiologic methods applied to clinical work and that, "to cure or alleviate human disease, research must begin and end by direct studies upon real people."

This volume should be read by every teacher of medicine or physiology who is not familiar with it and reread by those who are.